Epidemiology and Prevention of Vaccine-Preventable Diseases



11th EDITION

Department of Health and Human Services
Centers for Disease Control and Prevention
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Epidemiology and Prevention of Vaccine-Preventable Diseases

11th EDITION

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On the cover

"Die Spanische Krankheit" ("The Spanish Flu") ink drawing by Alfred Kubin, circa 1920. Kubin (1877-1959) studied in Munich and was associated with German expressionism. He was a contemporary of Edvard Munch, who also recorded his experience with the 1918 influenza pandemic. This work illustrates the figure of Death and the victims of the influenza pandemic in a way similar to that used in European woodcuts to depict the bubonic plague centuries earlier. The drawing is in a private collection.

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Milestones in the History of Vaccination

400BCE	1100s	1721	1796
Hippocrates describes diphtheria, epidemic jaundice, and other conditions	Variolation for smallpox first reported in China	Variolation introduced into Great Britain	Edward Jenner inoculates James Phipps with cowpox, and calls the procedure vaccination ("vacca" is Latin for cow)

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1870	1884	1885	1887	1900
Louis Pasteur creates the first live attenuated bacterial vaccine (chicken cholera)	Pasteur creates the first live attenuated viral vaccine (rabies)	Pasteur first uses rabies vaccine in a human	Institut Pasteur established	Paul Ehrlich formulates receptor theory of immunity

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Milestones in the History of Vaccination

1927	1931	1936	1948	1954
Yellow fever virus isolated	Goodpasture describes a technique for viral culture in hens' eggs	Thomas Francis and Thomas Magill develop the first inactivated influenza vaccine	John Enders and colleagues isolate Lansing Type II poliovirus in human cell line	Enders and Peebles isolate measles virus Francis Field Trial of inactivated polio vaccine

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Milestones in the History of Vaccination

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Milestones in the History of Vaccination

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Vaccines and Related Products Distributed in the United States

Vaccine/Biologic	Brand Name	Manufacturer	Type	How Supplied
Diphtheria, Tetanus, acellular Pertussis	Infanrix®	GlaxoSmithKline	Inactivated	single-dose vial or syringe
Diphtheria, Tetanus, acellular Pertussis	Tripedia®	sanofi-pasteur	Inactivated	single-dose vial
Diphtheria, Tetanus, acellular Pertussis	Daptacel®	sanofi-pasteur	Inactivated	single-dose vial
Diphtheria, Tetanus, acellular Pertussis + Hib	TriHIBit®	sanofi-pasteur	Inactivated	single-dose vial
Diphtheria, Tetanus, acellular Pertussis +Hep B + IPV	Pediarix®	GlaxoSmithKline	Inactivated	single-dose vial or syringe
Diphtheria, Tetanus, acellular Pertussis + Hib + IPV	Pentacel®	sanofi-pasteur	Inactivated	single-dose vial
Diphtheria, Tetanus, acellular Pertussis + IPV	Kinrix®	GlaxoSmithKline	Inactivated	single-dose vial or syringe
Diphtheria, Tetanus (DT; ped <7yrs, P-free)	generic	sanofi-pasteur	Inactivated	single-dose vial
Tetanus, diphtheria, adsorbed (Td; >7yrs, P-free)	Decavac®	sanofi-pasteur	Inactivated	single-dose syringe
Tetanus, diphtheria, adsorbed (Td; >7yrs)	generic	Mass Biologic Labs	Inactivated	15-dose vial
Tetanus, diphtheria, acellular Pertussis (Tdap; 10-64 yrs)	Boostrix®	GlaxoSmithKline	Inactivated	single-dose vial or syringe
Tetanus, diphtheria, acellular Pertussis (Tdap; 11-64 yrs)	Adacel™	sanofi-pasteur	Inactivated	single-dose vial
Tetanus toxoid (TT; >7 yrs) adsorbed	generic	sanofi-pasteur	Inactivated	10-dose vial
Tetanus toxoid (TT; adult booster use only)	generic	sanofi-pasteur	Inactivated	15-dose vial
Tetanus immune globulin (TIG)	HyperTET™	Talecris	Human immunoglobulin	single-dose syringe
Haemophilus influenzae type b (PRP-T)	ActHIB®	sanofi-pasteur	Inactivated	single-dose vial
Haemophilus influenzae type b (HbOC)	HibTITER®	Wyeth	Inactivated	single-dose vial
Haemophilus influenzae type b (PRP-OMP)	PedvaxHIB®	Merck	Inactivated	single-dose vial
Haemophilus influenzae type b (PRP-OMP) + Hep B	Comvax®	Merck	Inactivated	single-dose vial
Hepatitis A: ped/adol & adult formulations	Havrix®	GlaxoSmithKline	Inactivated	single-dose vial or syringe
Hepatitis A: ped/adol & adult formulations	Vaqta®	Merck	Inactivated	single-dose vial or syringe
Hepatitis A immune globulin	GamaSTAN™	Talecris	Human immunoglobulin	2 mL and 10 mL vials
Hepatitis B: ped/adol & adult formulations	Engerix-B®	GlaxoSmithKline	Inactivated	single-dose vial or syringe
Hepatitis B: ped/adol & adult formulations	Recombivax HB®	Merck	Inactivated	single-dose vial
Hepatitis B dialysis formulation	Recombivax HB®	Merck	Inactivated	single-dose vial
Hepatitis B immune globulin (HBIG)	HyperHEP B™	Talecris	Human immunoglobulin	1 mL syringe, 1 mL or 5 mL vial
Hepatitis B immune globulin (HBIG): ped formulation	HyperHEP B™	Talecris	Human immunoglobulin	single-dose 0.5 mL neonatal syringe
Hepatitis B immune globulin (HBIG)	Nabi-HB®	Nabi	Human immunoglobulin	single-dose vial
Hepatitis A & B: adult formulation	Twinrix®	GlaxoSmithKline	Inactivated	single-dose vial or syringe
Human papillomavirus (HPV)	Gardasil®	Merck	Inactivated	single-dose vial or syringe
Influenza (trivalent inactivated influenza vaccine [TIV])	Fluarix®	GlaxoSmithKline	Inactivated	10 single-dose syringes
Influenza (live attenuated influenza vaccine [LAIV])	FluMist®	Medimmune	Live, intranasal	10 single-use sprayers
Influenza (TIV)	Afluria®	CSL Biotherapies	Inactivated	single-dose syringe & 10-dose vial
Influenza (TIV)	Fluvirin®	Novartis	Inactivated	single-dose syringe & 10-dose vial
Influenza (TIV)	Fluzone®	sanofi-pasteur	Inactivated	10-dose vial
Influenza (TIV; >36 mos; no preservative)	Fluzone®	sanofi-pasteur	Inactivated	single-dose syringe (0.5 mL)
Influenza (TIV; ped 6-35 mos; no preservative)	Fluzone®	sanofi-pasteur	Inactivated	single-dose syringe (0.25 mL)
Influenza (TIV; >18 yrs)	FluLaval™	GlaxoSmithKline	Inactivated	10-dose vial
Measles, Mumps, Rubella (MMR)	M-M-R II®	Merck	Live, attenuated	single-dose vial
Measles, Mumps, Rubella + Varicella (MMRV)	ProQuad®	Merck	Live, attenuated	single-dose vial
Meningococcal conjugate (A/C/Y/W-135)	Menactra®	sanofi pasteur	Inactivated	single-dose vial
Meningococcal polysaccharide (A/C/Y/W-135)	Menomune®	sanofi pasteur	Inactivated	single-dose vial
Pneumococcal conjugate, 7-valent	Prevnar®	Wyeth	Inactivated	single-dose vial
Pneumococcal polysaccharide, 23-valent	Pneumovax 23®	Merck	Inactivated	single-dose vial or 5-dose vial
Polio (IPV)	IPOL®	sanofi pasteur	Inactivated	single-dose syringe or 10-dose vial
Rotavirus	RotaTeq®	Merck	Live, oral	single-dose tube
Rotavirus	Rotarix®	GlaxoSmithKline	Live, oral	single-dose tube
Varicella	Varivax®	Merck	Live, attenuated	single-dose vial
Varicella Zoster Immune Globulin (VZIG) (IND)	VariZIG™	Cangene	Human Immunoglobulin	125-U vial
Zoster	Zostavax®	Merck	Live, attenuated	single-dose vial
Anthrax, adsorbed	BioThrax™	BioPort	Inactivated	multi-dose vial
Japanese encephalitis	JE-VAX®	sanofi pasteur	Inactivated	single-dose vial
Rabies	Imovax®	sanofi pasteur	Inactivated	single-dose vial
Rabies	RabAvert®	Novartis	Inactivated	single-dose vial
Rabies Immune Globulin (RIG)	Imogam Rabies-HT®	sanofi-pasteur	Human immunoglobulin	2 mL and 10 mL vials
Rabies Immune Globulin (RIG)	HyperRAB™	Talecris	Human immunoglobulin	2 mL and 10 mL vials
Typhoid VI polysaccharide	Typhim Vi®	sanofi-pasteur	Inactivated	single-dose syringe and 20-dose vial
Typhoid, live oral Ty21a	Vivotif®	Berna	Live, attenuated	4-capsule package
Yellow Fever	YF-Vax®	sanofi-pasteur	Live, attenuated	single- and 5-dose vial

Principles of Vaccination

Immunology and Vaccine-Preventable Diseases

Immunology is a complicated subject, and a detailed discussion of it is beyond the scope of this text. However, an understanding of the basic function of the immune system is useful in order to understand both how vaccines work and the basis of recommendations for their use. The description that follows is simplified. Many excellent immunology textbooks are available to provide additional detail.

Immunity is the ability of the human body to tolerate the presence of material indigenous to the body ("self"), and to eliminate foreign ("nonself") material. This discriminatory ability provides protection from infectious disease, since most microbes are identified as foreign by the immune system. Immunity to a microbe is usually indicated by the presence of antibody to that organism. Immunity is generally specific to a single organism or group of closely related organisms. There are two basic mechanisms for acquiring immunity, active and passive.

Active immunity is protection that is produced by the person's own immune system. This type of immunity is usually permanent.

Passive immunity is protection by products produced by an animal or human and transferred to another human, usually by injection. Passive immunity often provides effective protection, but this protection wanes (disappears) with time, usually within a few weeks or months.

The immune system is a complex system of interacting cells whose primary purpose is to identify foreign ("nonself") substances referred to as antigens. Antigens can be either live (such as viruses and bacteria) or inactivated. The immune system develops a defense against the antigen. This defense is known as the immune response and usually involves the production of protein molecules by B lymphocytes, called antibodies (or immunoglobulins), and of specific cells (also known as cell-mediated immunity) whose purpose is to facilitate the elimination of foreign substances.

The most effective immune responses are generally produced in response to a live antigen. However, an antigen does not necessarily have to be alive, as occurs with infection with a virus or bacterium, to produce an immune response. Some proteins, such as hepatitis B surface antigen, are easily recognized by the immune system. Other material, such as polysaccharide (long chains of sugar molecules that make up the cell wall of certain bacteria) are less effective antigens, and the immune response may not provide as good protection.

Principles of Vaccination

Immunity
- Self vs. nonself
- Protection from infectious disease
- Usually indicated by the presence of antibody
- Very specific to a single organism

Principles of Vaccination

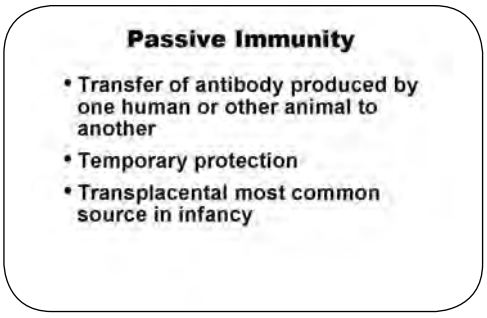
Active Immunity
- Protection produced by the person's own immune system
- Usually permanent

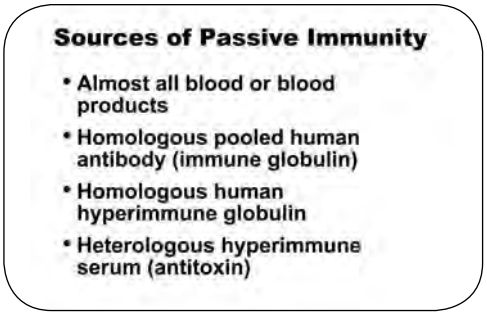
Passive Immunity
- Protection transferred from another human or animal
- Temporary protection that wanes with time

Principles of Vaccination

Antigen
- A live or inactivated substance (e.g., protein, polysaccharide) capable of producing an immune response

Antibody
- Protein molecules (immunoglobulin) produced by B lymphocytes to help eliminate an antigen





Passive Immunity

Passive immunity is the transfer of antibody produced by one human or other animal to another. Passive immunity provides protection against some infections, but this protection is temporary. The antibodies will degrade during a period of weeks to months, and the recipient will no longer be protected.

The most common form of passive immunity is that which an infant receives from its mother. Antibodies are transported across the placenta during the last 1–2 months of pregnancy. As a result, a full-term infant will have the same antibodies as its mother. These antibodies will protect the infant from certain diseases for up to a year. Protection is better against some diseases (e.g., measles, rubella, tetanus) than others (e.g., polio, pertussis).

Many types of blood products contain antibody. Some products (e.g., washed or reconstituted red blood cells) contain a relatively small amount of antibody, and some (e.g., intravenous immune globulin and plasma products) contain a large amount.

In addition to blood products used for transfusion (e.g., whole blood, red cells, and platelets) there are three major sources of antibody used in human medicine. These are homologous pooled human antibody, homologous human hyperimmune globulin, and heterologous hyperimmune serum.

Homologous pooled human antibody is also known as immune globulin. It is produced by combining (pooling) the IgG antibody fraction from thousands of adult donors in the United States. Because it comes from many different donors, it contains antibody to many different antigens. It is used primarily for postexposure prophylaxis for hepatitis A and measles and treatment of certain congenital immunoglobulin deficiencies.

Homologous human hyperimmune globulins are antibody products that contain high titers of specific antibody. These products are made from the donated plasma of humans with high levels of the antibody of interest. However, since hyperimmune globulins are from humans, they also contain other antibodies in lesser quantities. Hyperimmune globulins are used for postexposure prophylaxis for several diseases, including hepatitis B, rabies, tetanus, and varicella.

Heterologous hyperimmune serum is also known as antitoxin. This product is produced in animals, usually horses (equine), and contains antibodies against only one antigen. In the United States, antitoxin is available for treatment of botulism and diphtheria. A problem with this product is serum sickness, an immune reaction to the horse protein.

Immune globulin from human sources is polyclonal; it contains many different kinds of antibodies. In the 1970s, techniques were developed to isolate and "immortalize" (cause to grow indefinitely) single B cells, which led to the development of monoclonal antibody products. Monoclonal antibody is produced from a single clone of B cells, so these products contain antibody to only one antigen or closely related group of antigens. Monoclonal antibody products have many applications, including the diagnosis of certain types of cancer (colorectal, prostate, ovarian, breast), treatment of cancer (B-cell chronic lymphocytic leukemia, non-Hodgkin lymphoma), prevention of transplant rejection, and treatment of autoimmune diseases (Crohn disease, rheumatoid arthritis) and infectious diseases.

Monoclonal Antibody

- Derived from a single type, or clone, of antibody-producing cells (B cells)
- Antibody is specific to a single antigen or closely related group of antigens
- Used for diagnosis and therapy of certain cancers and autoimmune and infectious diseases

A monoclonal antibody product is available for the prevention of respiratory syncytial virus (RSV) infection. It is called palivizumab (Synagis). Palivizumab is a humanized monoclonal antibody specific for RSV. It does not contain any other antibody except RSV antibody, and so will not interfere with the response to a live virus vaccine.

Antibody for Prevention of RSV

- Palivizumab (Synagis)
  - —monoclonal
  - —contains only RSV antibody
  - —will not interfere with the response to a live virus vaccine

Active Immunity

Active immunity is stimulation of the immune system to produce antigen-specific humoral (antibody) and cellular immunity. Unlike passive immunity, which is temporary, active immunity usually lasts for many years, often for a lifetime.

One way to acquire active immunity is to survive infection with the disease-causing form of the organism. In general, once persons recover from infectious diseases, they will have lifelong immunity to that disease. The persistence of protection for many years after the infection is known as immunologic memory. Following exposure of the immune system to an antigen, certain cells (memory B cells) continue to circulate in the blood (and also reside in the bone marrow) for many years. Upon reexposure to the antigen, these memory cells begin to replicate and produce antibody very rapidly to reestablish protection.

Vaccination

- Active immunity produced by vaccine
- Immunity and immunologic memory similar to natural infection but without risk of disease

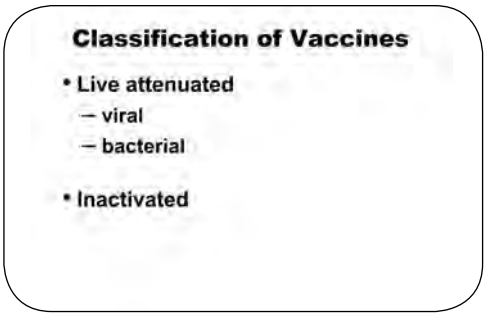
Another way to produce active immunity is by vaccination. Vaccines interact with the immune system and often produce an immune response similar to that produced by the natural infection, but they do not subject the recipient to the disease and its potential complications. Many vaccines also produce immunologic memory similar to that acquired by having the natural disease.

Many factors may influence the immune response to vaccination. These include the presence of maternal antibody, nature and dose of antigen, route of administration, and the presence of an adjuvant (e.g., aluminum-containing material

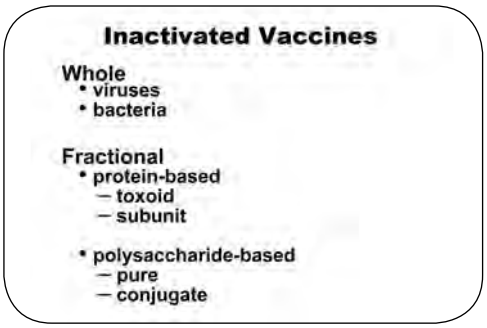
added to improve the immunogenicity of the vaccine). Host factors such as age, nutritional factors, genetics, and coexisting disease, may also affect the response.

Classification of Vaccines

There are two basic types of vaccines: live attenuated and inactivated. The characteristics of live and inactivated vaccines are different, and these characteristics determine how the vaccine is used.



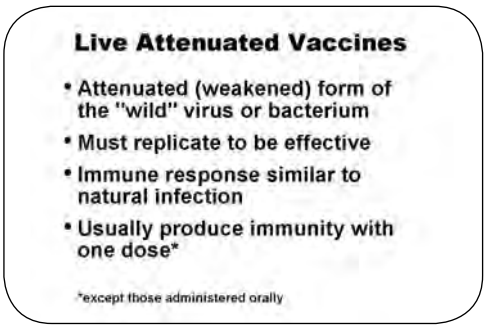
Live attenuated vaccines are produced by modifying a disease-producing ("wild") virus or bacterium in a laboratory. The resulting vaccine organism retains the ability to replicate (grow) and produce immunity, but usually does not cause illness. The majority of live attenuated vaccines available in the United States contain live viruses. However, one live attenuated bacterial vaccine is available.



Inactivated vaccines can be composed of either whole viruses or bacteria, or fractions of either. Fractional vaccines are either protein-based or polysaccharide-based. Protein-based vaccines include toxoids (inactivated bacterial toxin) and subunit or subvirion products. Most polysaccharide-based vaccines are composed of pure cell wall polysaccharide from bacteria. Conjugate polysaccharide vaccines contain polysaccharide that is chemically linked to a protein. This linkage makes the polysaccharide a more potent vaccine.

GENERAL RULE

The more similar a vaccine is to the disease-causing form of the organism, the better the immune response to the vaccine.



Live Attenuated Vaccines

Live vaccines are derived from "wild," or disease-causing, viruses or bacteria. These wild viruses or bacteria are attenuated, or weakened, in a laboratory, usually by repeated culturing. For example, the measles virus used as a vaccine today was isolated from a child with measles disease in 1954. Almost 10 years of serial passage using tissue culture media was required to transform the wild virus into attenuated vaccine virus.

To produce an immune response, live attenuated vaccines must replicate (grow) in the vaccinated person. A relatively

small dose of virus or bacteria is administered, which replicates in the body and creates enough of the organism to stimulate an immune response. Anything that either damages the live organism in the vial (e.g., heat, light) or interferes with replication of the organism in the body (circulating antibody) can cause the vaccine to be ineffective.

Although live attenuated vaccines replicate, they usually do not cause disease such as may occur with the "wild" form of the organism. When a live attenuated vaccine does cause "disease," it is usually much milder than the natural disease and is referred to as an adverse reaction.

The immune response to a live attenuated vaccine is virtually identical to that produced by a natural infection. The immune system does not differentiate between an infection with a weakened vaccine virus and an infection with a wild virus. Live attenuated vaccines produce immunity in most recipients with one dose, except those administered orally. However, a small percentage of recipients do not respond to the first dose of an injected live vaccine (such as MMR or varicella) and a second dose is recommended to provide a very high level of immunity in the population.

Live attenuated vaccines may cause severe or fatal reactions as a result of uncontrolled replication (growth) of the vaccine virus. This only occurs in persons with immunodeficiency (e.g., from leukemia, treatment with certain drugs, or human immunodeficiency virus (HIV) infection).

A live attenuated vaccine virus could theoretically revert to its original pathogenic (disease-causing) form. This is known to happen only with live (oral) polio vaccine.

Active immunity from a live attenuated vaccine may not develop because of interference from circulating antibody to the vaccine virus. Antibody from any source (e.g., transplacental, transfusion) can interfere with replication of the vaccine organism and lead to poor response or no response to the vaccine (also known as vaccine failure). Measles vaccine virus seems to be most sensitive to circulating antibody. Polio and rotavirus vaccine viruses are least affected.

Live attenuated vaccines are fragile and can be damaged or destroyed by heat and light. They must be handled and stored carefully.

Currently available live attenuated viral vaccines are measles, mumps, rubella, vaccinia, varicella, zoster (which contains the same virus as varicella vaccine but in much higher amount), yellow fever, rotavirus, and influenza (intranasal). Oral polio vaccine is a live viral vaccine but is no longer available in the United States. Live attenuated bacterial vaccines are bacille Calmette-Guérin (BCG—not currently available in the U.S.) and oral typhoid vaccine.

Live Attenuated Vaccines

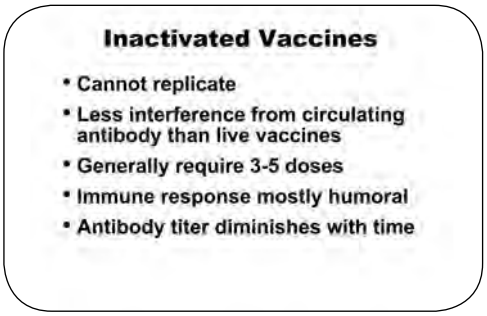
- Severe reactions possible
- Interference from circulating antibody
- Fragile – must be stored and handled carefully

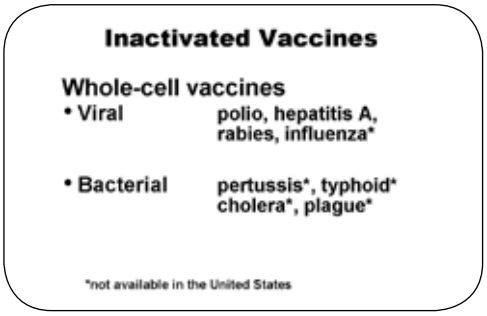
Live Attenuated Vaccines

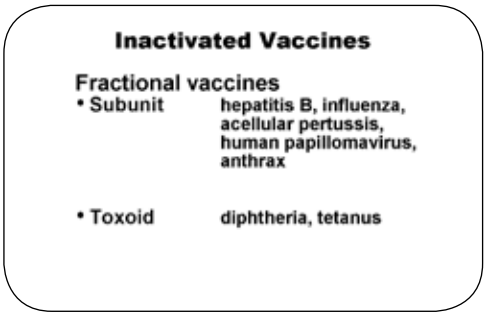
• Viral	measles, mumps, rubella, vaccinia, varicella, zoster, yellow fever, rotavirus, intranasal influenza, oral polio*
• Bacterial	BCG*, oral typhoid

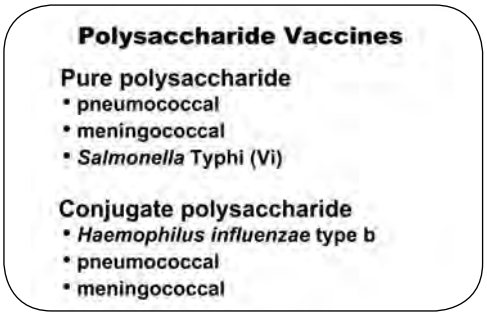
*not available in the United States

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Inactivated Vaccines

Inactivated vaccines are produced by growing the bacterium or virus in culture media, then inactivating it with heat and/or chemicals (usually formalin). In the case of fractional vaccines, the organism is further treated to purify only those components to be included in the vaccine (e.g., the polysaccharide capsule of pneumococcus).

Inactivated vaccines are not alive and cannot replicate. The entire dose of antigen is administered in the injection. These vaccines cannot cause disease from infection, even in an immunodeficient person. Inactivated antigens are less affected by circulating antibody than are live agents, so they may be given when antibody is present in the blood (e.g., in infancy or following receipt of antibody-containing blood products).

Inactivated vaccines always require multiple doses. In general, the first dose does not produce protective immunity, but "primes" the immune system. A protective immune response develops after the second or third dose. In contrast to live vaccines, in which the immune response closely resembles natural infection, the immune response to an inactivated vaccine is mostly humoral. Little or no cellular immunity results. Antibody titers against inactivated antigens diminish with time. As a result, some inactivated vaccines may require periodic supplemental doses to increase, or "boost," antibody titers.

Currently available whole-cell inactivated vaccines are limited to inactivated whole viral vaccines (polio, hepatitis A, and rabies). Inactivated whole virus influenza vaccine and whole inactivated bacterial vaccines (pertussis, typhoid, cholera, and plague) are no longer available in the United States. Fractional vaccines include subunits (hepatitis B, influenza, acellular pertussis, human papillomavirus, anthrax) and toxoids (diphtheria, tetanus). A subunit vaccine for Lyme disease is no longer available in the United States.

Polysaccharide Vaccines

Polysaccharide vaccines are a unique type of inactivated subunit vaccine composed of long chains of sugar molecules that make up the surface capsule of certain bacteria. Pure polysaccharide vaccines are available for three diseases: pneumococcal disease, meningococcal disease, and *Salmonella* Typhi. A pure polysaccharide vaccine for *Haemophilus influenzae* type b (Hib) is no longer available in the United States.

The immune response to a pure polysaccharide vaccine is typically T-cell independent, which means that these vaccines are able to stimulate B cells without the assistance of T-helper cells. T-cell–independent antigens, including

polysaccharide vaccines, are not consistently immunogenic in children younger than 2 years of age. Young children do not respond consistently to polysaccharide antigens, probably because of immaturity of the immune system.

Repeated doses of most inactivated protein vaccines cause the antibody titer to go progressively higher, or "boost." This does not occur with polysaccharide antigens; repeat doses of polysaccharide vaccines usually do not cause a booster response. Antibody induced with polysaccharide vaccines has less functional activity than that induced by protein antigens. This is because the predominant antibody produced in response to most polysaccharide vaccines is IgM, and little IgG is produced.

In the late 1980s, it was discovered that the problems noted above could be overcome through a process called conjugation, in which the polysaccharide is chemically combined with a protein molecule. Conjugation changes the immune response from T-cell independent to T-cell dependent, leading to increased immunogenicity in infants and antibody booster response to multiple doses of vaccine.

The first conjugated polysaccharide vaccine was for Hib. A conjugate vaccine for pneumococcal disease was licensed in 2000. A meningococcal conjugate vaccine was licensed in 2005.

Pure Polysaccharide Vaccines

- Not consistently immunogenic in children younger than 2 years of age
- No booster response
- Antibody with less functional activity
- Immunogenicity improved by conjugation

Recombinant Vaccines

Vaccine antigens may also be produced by genetic engineering technology. These products are sometimes referred to as recombinant vaccines. Four genetically engineered vaccines are currently available in the United States. Hepatitis B and human papillomavirus (HPV) vaccines are produced by insertion of a segment of the respective viral gene into the gene of a yeast cell. The modified yeast cell produces pure hepatitis B surface antigen or HPV capsid protein when it grows. Live typhoid vaccine (Ty21a) is *Salmonella* Typhi bacteria that have been genetically modified to not cause illness. Live attenuated influenza vaccine has been engineered to replicate effectively in the mucosa of the nasopharynx but not in the lungs.

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Plotkin S. Correlates of vaccine-induced immunity. *Clin Infect Dis* 2008; 47:401–9

Principles of Vaccination

1

General Recommendations on Immunization

This chapter discusses issues that are commonly encountered in vaccination practice. A more thorough discussion of issues common to more than one vaccine can be found in the *General Recommendations on Immunization: Recommendations of the Advisory Committee on Immunization Practices*. These recommendations are revised every 3 to 5 years as needed; the most current edition was published in December 2006 (*MMWR* 2006;55[RR-15]:1–48). A revised version is expected to be published in late 2009 or early 2010. All providers who administer vaccine should have a copy of this report and be familiar with its content. It can be downloaded from the *MMWR* website or ordered in print version from the Centers for Disease Control and Prevention.

Timing and Spacing of Vaccines

The timing and spacing of vaccine doses are two of the most important issues in the appropriate use of vaccines. Specific circumstances that are commonly encountered in immunization practice are the timing of antibody-containing blood products and live vaccines (particularly measles and varicella-containing vaccines), simultaneous and nonsimultaneous administration of different vaccines, and the interval between subsequent doses of the same vaccine.

GENERAL RULE

> Inactivated vaccines generally are not affected by circulating antibody to the antigen.
>
> Live attenuated vaccines may be affected by circulating antibody to the antigen.

Antibody–Vaccine Interactions

The presence of circulating antibody to a vaccine antigen may reduce or completely eliminate the immune response to the vaccine. The amount of interference produced by circulating antibody generally depends on the type of vaccine administered and the amount of antibody.

Inactivated antigens are generally not affected by circulating antibody, so they can be administered before, after, or at the same time as the antibody. Simultaneous administration of antibody (in the form of immune globulin) and vaccine is recommended for postexposure prophylaxis of certain diseases, such as hepatitis B, rabies, and tetanus.

Antibody and Measles- and Varicella-Containing* Vaccines

Product Given First	Action
Vaccine	Wait 2 weeks before giving antibody
Antibody	Wait 3 months or longer before giving vaccine

*except zoster vaccine

Live Injected Vaccines

Live vaccines must replicate in order to cause an immune response. Antibody against injected live vaccine antigen may interfere with replication. If a live injectable vaccine (measles-mumps-rubella [MMR], varicella, or combination measles-mumps-rubella-varicella [MMRV]) must be given around the time that antibody is given, the two must be separated by enough time so that the antibody does not interfere with viral replication. If the live vaccine is given first, it is necessary to wait at least 2 weeks (i.e., an incubation period) before giving the antibody. If the interval between the vaccine and antibody is less than 2 weeks, the recipient should be tested for immunity or the vaccine dose should be repeated.

If the antibody is given before a dose of MMR or varicella vaccine, it is necessary to wait until the antibody has waned (degraded) before giving the vaccine to reduce the chance of interference by the antibody. The necessary interval between an antibody-containing product and MMR or varicella-containing vaccine (except zoster vaccine) depends on the concentration of antibody in the product, but is always 3 months or longer. A table listing the recommended intervals between administration of antibody products and live vaccines (MMR and varicella-containing) is included in Appendix A and in the *General Recommendations on Immunization* (2006). The interval between administration of an antibody product and MMR or varicella vaccination can be as long as 11 months. Zoster vaccine is not known to be affected by circulating antibody so it can be administered at any time before or after receipt of an antibody-containing blood product.

Although passively acquired antibodies can interfere with the response to rubella vaccine, the low dose of anti-Rho(D) globulin administered to postpartum women has not been demonstrated to reduce the response to the rubella vaccine. Because of the importance of rubella and varicella immunity among childbearing age women, women without evidence of immunity to rubella or varicella should receive MMR or varicella vaccine (but not MMRV) in the postpartum period. Vaccination should not be delayed because of receipt of anti-Rho(D) globulin or any other blood product during the last trimester of pregnancy or at delivery. These women should be vaccinated immediately after delivery and, if possible, tested 3 months later to ensure immunity to rubella and, if necessary, to measles.

Live Oral and Intranasal Vaccines

Oral typhoid and yellow fever vaccines are not known to be affected by the administration of immune globulin or blood products. This is because few North Americans are immune

to yellow fever or typhoid. Consequently, donated blood products in the United States do not contain a significant amount of antibody to these organisms. Typhoid and yellow fever vaccines may be given simultaneously with blood products, or separated by any interval. The replication of live attenuated influenza (LAIV) and rotavirus vaccines are not believed to be affected by antibody-containing blood products. These can be given any time before or after administration of antibody-containing blood products.

Products Containing Type-Specific or Negligible Antibody

Some blood products do not contain antibodies that interfere with vaccine replication. Palivizumab (Synagis), used for the prevention of respiratory syncytial virus (RSV) infection in infants and young children, contains antibody directed only at RSV. Washed red blood cells contain a negligible amount of antibody. These products can be given anytime before or after administration of MMR or varicella-containing vaccines.

Products Containing Type-Specific or Negligible Antibody

- Palivizumab (Synagis)
  - —monoclonal
  - —contains only RSV antibody
- Red blood cells (RBCs), washed
  - —negligible antibody content

Simultaneous and Nonsimultaneous Administration

GENERAL RULE

All vaccines can be administered at the same visit as all other vaccines.

Simultaneous administration (that is, administration on the same day) of the most widely used live and inactivated vaccines does not result in decreased antibody responses or increased rates of adverse reaction. Simultaneous administration of all vaccines for which a child is eligible is very important in childhood vaccination programs because it increases the probability that a child will be fully immunized at the appropriate age. A study during a measles outbreak in the early 1990s showed that about one-third of measles cases in unvaccinated but vaccine-eligible preschool children could have been prevented if MMR had been administered at the same visit when another vaccine was given.

Although all indicated vaccines should be administered at the same visit, individual vaccines should not be mixed in the same syringe unless they are licensed for mixing by the Food and Drug Administration. Only the sanofi-pasteur DTaP/Hib (TriHIBit) and DTaP-IPV/Hib (Pentacel) vaccines are licensed for mixing in the same syringe. See Appendix D for additional guidelines for vaccine administration.

Spacing of Vaccine Combinations Not Given Simultaneously

Combination	Minimum Interval
Two live parenteral, or live intranasal influenza vaccine	4 weeks
All other	None

Spacing of Live Vaccines not Given Simultaneously

- If two live parenteral vaccines, or live intranasal influenza vaccine, are given less than 4 weeks apart the vaccine given second should be repeated
- Exception is yellow fever vaccine given less than 4 weeks after measles vaccine

Nonsimultaneous Administration of Different Vaccines

In some situations, vaccines that could be given at the same visit are not. If live parenteral (injected) vaccines (MMR, MMRV, varicella, zoster, and yellow fever) and live intranasal influenza vaccine (LAIV) are not administered at the same visit, they should be separated by at least 4 weeks. This interval is intended to reduce or eliminate interference from the vaccine given first on the vaccine given later. If two live parenteral vaccines or LAIV are not administered on the same day but are separated by less than 4 weeks, the vaccine given second should be repeated in 4 weeks or confirmed to have been effective by serologic testing of the recipient (serologic testing is not recommended following LAIV, varicella, or zoster vaccines). An exception to this recommendation is yellow fever vaccine administered less than 4 weeks after single-antigen measles vaccine. A 1999 study demonstrated that yellow fever vaccine is not affected by measles vaccine given 1–27 days earlier. The effect of nonsimultaneously administered rubella, mumps, varicella, zoster, LAIV and yellow fever vaccines is not known.

Live vaccines administered by the oral route (oral polio vaccine [OPV] oral typhoid, and rotavirus) are not believed to interfere with each other if not given simultaneously. These vaccines may be given at any time before or after each other. Rotavirus vaccine is not approved for children older than 32 weeks, oral typhoid is not approved for children younger than 6 years of age, and OPV is no longer available in the United States, so these vaccines are not likely to be given to the same child.

Parenteral live vaccines (MMR, MMRV, varicella, zoster, and yellow fever) and LAIV are not believed to have an effect on live vaccines given by the oral route (OPV, oral typhoid, and rotavirus). Live oral vaccines may be given at any time before or after live parenteral vaccines or LAIV.

All other combinations of two inactivated vaccines, or live and inactivated vaccines, may be given at any time before or after each other.

Interval Between Doses of the Same Vaccine

GENERAL RULE

Increasing the interval between doses of a multidose vaccine does not diminish the effectiveness of the vaccine.

Decreasing the interval between doses of a multidose vaccine may interfere with antibody response and protection.

Immunizations are recommended for members of the youngest age group at risk for a disease for whom efficacy and safety of a vaccine have been demonstrated. Most vaccines in the childhood immunization schedule require two or more doses for development of an adequate and persisting antibody response. Studies have demonstrated that recommended ages and intervals between doses of the same antigen(s) provide optimal protection or have the best evidence of efficacy. Table 1 of the *General Recommendations on Immunization* (included in Appendix A) shows the recommended and minimal ages and intervals between doses of vaccines most frequently used in the United States.

Administering doses of a multidose vaccine at shorter than the recommended intervals might be necessary when an infant or child is behind schedule and needs to be brought up-to-date quickly or when international travel is pending. In these cases, an accelerated schedule using the minimum age or minimum interval criteria can be used. Accelerated schedules should not be used routinely.

Minimum Intervals and Ages

Vaccine doses should not be administered at intervals less than the minimum intervals or earlier than the minimum age

Vaccine doses should not be administered at intervals less than the recommended minimal intervals or earlier than the minimal ages. Two exceptions to this may occur. The first is for measles vaccine during a measles outbreak, when the vaccine may be administered at an age younger than 12 months (this dose would not be counted, and should be repeated at 12 months of age or older). The second exception involves administering a dose a few days earlier than the minimum interval or age, which is unlikely to have a substantially negative effect on the immune response to that dose. Although vaccinations should not be scheduled at an interval or age less than the recommended minimums, a child may have erroneously been brought to the office early, or may have come for an appointment not specifically for vaccination. In these situations, the clinician can consider administering the vaccine earlier than the minimum interval or age. If the parent/child is known to the clinician and is reliable, it is preferable to reschedule the child for vaccination closer to the recommended interval. If the parent/child is not known to the clinician or is not reliable (e.g., habitually misses appointments), it may be preferable to administer the vaccine at that visit than to reschedule a later appointment that may not be kept.

Vaccine doses administered up to 4 days before the minimum interval or age can be counted as valid. This 4-day recommendation does not apply to rabies vaccine because of the unique schedule for this vaccine. Doses administered 5 days or earlier than the minimum interval or age should not be counted as valid doses and should be repeated as age appropriate. The repeat dose should generally be spaced after the invalid dose by an interval at least equal to the

Violation of Minimum Intervals or Minimum Age

- ACIP recommends that vaccine doses given up to 4 days before the minimum interval or age be counted as valid
- Immunization programs and/or school entry requirements may not accept all doses given earlier than the minimum age or interval

Extended Interval Between Doses

- Not all permutations of all schedules for all vaccines have been studied
- Available studies of extended intervals have shown no significant difference in final titer
- It is not necessary to restart the series or add doses because of an extended interval between doses

recommended minimum interval shown in Table 1 of the General Recommendations. In certain situations, local or state requirements might mandate that doses of selected vaccines be administered on or after specific ages, superseding this 4-day "grace period."

In some cases, a scheduled dose of vaccine may not be given on time. If this occurs, the dose should be given at the next visit. Not all permutations of all schedules for all vaccines have been studied. However, available data indicate that intervals between doses longer than those routinely recommended do not affect seroconversion rate or titer when the schedule is completed. Consequently, it is not necessary to restart the series or add doses of any vaccine because of an extended interval between doses. The only exception to this rule is oral typhoid vaccine in some circumstances. Some experts recommend repeating the series of oral typhoid vaccine if the four-dose series is extended to more than 3 weeks.

Number of Doses

For live injected vaccines, the first dose administered at the recommended age usually provides protection. An additional dose is given to provide another opportunity for vaccine response in the small proportion of recipients who do not respond to the first dose. For instance, 95%–98% of recipients will respond to a single dose of measles vaccine. The second dose is given to ensure that nearly 100% of persons are immune (i.e., the second dose is "insurance"). Immunity following live vaccines is long-lasting, and booster doses are not necessary.

For inactivated vaccines, the first dose administered at the recommended age usually does not provide protection (hepatitis A vaccine is an exception). A protective immune response may not develop until the second or third dose. For inactivated vaccines, antibody titers may decrease (wane) below protective levels after a few years. This phenomenon is most notable for tetanus and diphtheria. For these vaccines, periodic "boosting" is required. An additional dose is given to raise antibody back to protective levels.

Not all inactivated vaccines require boosting throughout life. For example, *Haemophilus influenzae* type b (Hib) vaccine does not require boosting because Hib disease is very rare in children older than 5 years of age. Hepatitis B vaccine does not require boosting because of immunologic memory to the vaccine and the long incubation period of hepatitis B (which can produce an "autoboost").

Adverse Reactions Following Vaccination

Vaccines are intended to produce active immunity to specific antigens. An adverse reaction is an untoward effect caused by a vaccine that is extraneous to the vaccine's primary purpose of producing immunity. Adverse reactions are also called vaccine side effects. A vaccine adverse event refers to any medical event that occurs following vaccination. An adverse event could be a true adverse reaction or just a coincidental event, with further research needed to distinguish between them.

Vaccine Adverse Reactions

- Adverse reaction
  - extraneous effect *caused by vaccine*
  - side effect
- Adverse event
  - *any* event following vaccination
  - may be true adverse reaction
  - may be only coincidental

Vaccine adverse reactions fall into three general categories: local, systemic, and allergic. Local reactions are generally the least severe and most frequent. Allergic reactions are the most severe and least frequent.

The most common type of adverse reactions are local reactions, such as pain, swelling, and redness at the site of injection. Local reactions may occur with up to 80% of vaccine doses, depending on the type of vaccine. Local reactions are most common with inactivated vaccines, particularly those, such as DTaP, that contain an adjuvant. Local adverse reactions generally occur within a few hours of the injection and are usually mild and self-limited. On rare occasions, local reactions may be very exaggerated or severe. These are often referred to as hypersensitivity reactions, although they are not allergic, as the term implies. These reactions are also known as Arthus reactions, and are most commonly seen with tetanus and diphtheria toxoids. Arthus reactions are believed to be due to very high titers of antibody, usually caused by too many doses of toxoid.

Vaccine Adverse Reactions

- Local
  - pain, swelling, redness at site of injection
  - common with inactivated vaccines
  - usually mild and self-limited

Systemic adverse reactions are more generalized events and include fever, malaise, myalgias (muscle pain), headache, loss of appetite, and others. These symptoms are common and nonspecific; they may occur in vaccinated persons because of the vaccine or may be caused by something unrelated to the vaccine, like a concurrent viral infection, stress, or excessive alcohol consumption.

Vaccine Adverse Reactions

- Systemic
  - fever, malaise, headache
  - nonspecific
  - may be unrelated to vaccine

Systemic adverse reactions were relatively frequent with DTP vaccine, which contained a whole-cell pertussis component. However, comparison of the frequency of systemic adverse events among vaccine and placebo recipients shows they are less common with inactivated vaccines currently in use, including acellular pertussis vaccine.

Systemic adverse reactions may occur following receipt of live attenuated vaccines. Live attenuated vaccines must replicate in order to produce immunity. The adverse reactions that follow live attenuated vaccines, such as fever or rash, represent symptoms produced from viral replication and are similar to a mild form of the natural

Live Attenuated Vaccines

- Must replicate to produce immunity
- Symptoms usually mild
- Occur after an incubation period (usually 7-21 days)

disease. Systemic adverse reactions following live vaccines are usually mild, and occur 7–21 days after the vaccine was given (i.e., after an incubation period of the vaccine virus). LAIV replicates in the mucous membranes of the nose and throat, not in the lung. As a result, LAIV may cause upper respiratory symptoms (like a cold) but not influenza-like symptoms.

A third type of vaccine adverse reaction is a severe (anaphylactic) allergic reaction. The allergic reaction may be caused by the vaccine antigen itself or some other component of the vaccine, such as cell culture material, stabilizer, preservative, or antibiotic used to inhibit bacterial growth. Severe allergic reactions may be life-threatening. Fortunately, they are rare, occurring at a rate of less than one in half a million doses. The risk of an allergic reaction can be minimized by good screening prior to vaccination. All providers who administer vaccines must have an emergency protocol and supplies to treat anaphylaxis.

Reporting Vaccine Adverse Events

Vaccine Adverse Reactions

- Allergic
  - due to vaccine or vaccine component
  - rare
  - risk minimized by screening

From 1978 to 1990, CDC conducted the Monitoring System for Adverse Events Following Immunization (MSAEFI) in the public sector. In 1990, MSAEFI was replaced by the Vaccine Adverse Event Reporting System (VAERS), which includes reporting from both public and private sectors. Providers should report any clinically significant adverse event that occurs after the administration of any vaccine licensed in the United States.

Providers should report a clinically significant adverse event even if they are unsure whether a vaccine caused the event. The telephone number to call for answers to questions and to obtain VAERS forms is (800) 822-7967, or visit the VAERS website at http://vaers.hhs.gov. VAERS now accepts reports of adverse reactions through their online system. (See Chapter 4, Vaccine Safety.)

Contraindications and Precautions to Vaccination

Contraindication

- A condition in a recipient that greatly increases the chance of a serious adverse reaction

Contraindications and precautions to vaccination generally dictate circumstances when vaccines will not be given. Most contraindications and precautions are temporary, and the vaccine can be given at a later time.

A contraindication is a condition in a recipient that greatly increases the chance of a serious adverse reaction. It is a condition in the recipient of the vaccine, not with the vaccine per se. If the vaccine were given in the presence of that condition, the resulting adverse reaction could seriously harm the recipient. For instance, administering influenza vaccine to a person with a true anaphylactic allergy to

egg could cause serious illness or death in the recipient. In general, vaccines should not be administered when a contraindication condition is present.

A precaution is similar to a contraindication. A precaution is a condition in a recipient that *might increase* the chance or severity of a serious adverse reaction, or that might compromise the ability of the vaccine to produce immunity (such as administering measles vaccine to a person with passive immunity to measles from a blood transfusion). Injury could result, but the chance of this happening is less than with a contraindication. In general, vaccines are deferred when a precaution condition is present. However, situations may arise when the benefit of protection from the vaccine outweighs the risk of an adverse reaction, and a provider may decide to give the vaccine. For example, prolonged crying or a high fever after a dose of whole-cell or acellular pertussis vaccine is considered to be a precaution to subsequent doses of pediatric pertussis vaccine. But if the child were at high risk of pertussis exposure (e.g., during a pertussis outbreak in the community), a provider may choose to vaccinate the child and treat the adverse reaction if it occurs. In this example, the benefit of protection from the vaccine outweighs the harm potentially caused by the vaccine.

There are very few true contraindication and precaution conditions. Only two of these conditions are generally considered to be permanent: severe (anaphylactic) allergic reaction to a vaccine component or following a prior dose of a vaccine, and encephalopathy not due to another identifiable cause occurring within 7 days of pertussis vaccination.

Conditions considered permanent precautions to further doses of pediatric pertussis-containing vaccine are temperature of 105°F or higher within 48 hours of a dose, collapse or shock-like state (hypotonic hyporesponsive episode) within 48 hours of a dose, persistent inconsolable crying lasting 3 or more hours occurring within 48 hours of a dose, or a seizure, with or without fever, occurring within 3 days of a dose. The occurrence of one of these events in a child following DTaP vaccine is not a precaution to later vaccination with the adolescent/adult formulation of pertussis vaccine (Tdap).

Two conditions are temporary contraindications to vaccination with live vaccines: pregnancy and immunosuppression. Two conditions are temporary precautions to vaccination: moderate or severe acute illness (all vaccines), and recent receipt of an antibody-containing blood product. The latter precaution applies only to MMR and varicella-containing (except zoster) vaccines.

Precaution

- A condition in a recipient that might increase the chance or severity of an adverse reaction, or
- Might compromise the ability of the vaccine to produce immunity

Contraindications and Precautions

Permanent contraindications to vaccination:

- severe allergic reaction to a vaccine component or following a prior dose
- encephalopathy not due to another identifiable cause occurring within 7 days of pertussis vaccination

Contraindications and Precautions

Condition	Live	Inactivated
Allergy to component	C	C
Encephalopathy	---	C
Pregnancy	C	V*
Immunosuppression	C	V
Severe illness	P	P
Recent blood product	P**	V

C=contraindication P=precaution V=vaccinate if indicated
*except HPV and Tdap. **MMR and varicella-containing (except zoster vaccine), and rotavirus vaccines only

Allergy

A severe (anaphylactic) allergic reaction following a dose of vaccine will almost always contraindicate a subsequent dose of that vaccine. Severe allergies are those that are mediated by IgE, occur within minutes or hours of receiving the vaccine, and require medical attention. Examples of symptoms and signs typical of severe allergic reactions are generalized urticaria (hives), swelling of the mouth and throat, difficulty breathing, wheezing, hypotension, or shock. With appropriate screening these reactions are very rare following vaccination.

A table listing vaccine contents is included in Appendix B. Persons may be allergic to the vaccine antigen or to a vaccine component such as animal protein, antibiotic, preservative, or stabilizer. The most common animal protein allergen is egg protein found in vaccines prepared using embryonated chicken eggs (e.g., yellow fever and influenza vaccines). Ordinarily, a person who can eat eggs or egg products can receive vaccines that contain egg; persons with histories of anaphylactic or anaphylactic-like allergy to eggs or egg proteins should not. Asking persons whether they can eat eggs without adverse effects is a reasonable way to screen for those who might be at risk from receiving yellow fever and influenza vaccines.

Several recent studies have shown that children who have a history of severe allergy to eggs rarely have reactions to MMR vaccine. This is probably because measles and mumps vaccine viruses are both grown in chick embryo fibroblasts, not actually in eggs. It appears that gelatin, not egg, might be the cause of allergic reactions to MMR. As a result, in 1998, the ACIP removed severe egg allergy as a contraindication to measles and mumps vaccines. Egg-allergic children may be vaccinated with MMR without prior skin testing.

Certain vaccines contain trace amounts of neomycin. Persons who have experienced an anaphylactic reaction to neomycin should not receive these vaccines. Most often, neomycin allergy presents as contact dermatitis, a manifestation of a delayed-type (cell-mediated) immune response, rather than anaphylaxis. A history of delayed-type reactions to neomycin is not a contraindication for administration of vaccines that contain neomycin.

Latex is sap from the commercial rubber tree. Latex contains naturally occurring impurities (e.g., plant proteins and peptides), which are believed to be responsible for allergic reactions. Latex is processed to form natural rubber latex and dry natural rubber. Dry natural rubber and natural rubber latex might contain the same plant impurities as latex but in lesser amounts. Natural rubber latex is used to produce medical gloves, catheters, and other products. Dry natural rubber is used in syringe plungers, vial stoppers,

and injection ports on intravascular tubing. Synthetic rubber and synthetic latex also are used in medical gloves, syringe plungers, and vial stoppers. Synthetic rubber and synthetic latex do not contain natural rubber or natural latex, and therefore, do not contain the impurities linked to allergic reactions.

The most common type of latex sensitivity is contact-type (type 4) allergy, usually as a result of prolonged contact with latex-containing gloves. However, injection-procedure-associated latex allergies among diabetic patients have been described. Allergic reactions (including anaphylaxis) after vaccination procedures are rare. Only one report of an allergic reaction after administration of hepatitis B vaccine in a patient with known severe allergy (anaphylaxis) to latex has been published.

If a person reports a severe (anaphylactic) allergy to latex, vaccines supplied in vials or syringes that contain natural rubber should not be administered unless the benefit of vaccination clearly outweighs the risk of an allergic reaction to the vaccine. For latex allergies other than anaphylactic allergies (e.g., a history of contact allergy to latex gloves), vaccines supplied in vials or syringes that contain dry natural rubber or natural rubber latex can be administered.

Pregnancy

The concern with vaccination of a pregnant woman is infection of the fetus and is theoretical. Only smallpox (vaccinia) vaccine has been shown to cause fetal injury. However, since the theoretical possibility exists, live vaccines should not be administered to women known to be pregnant.

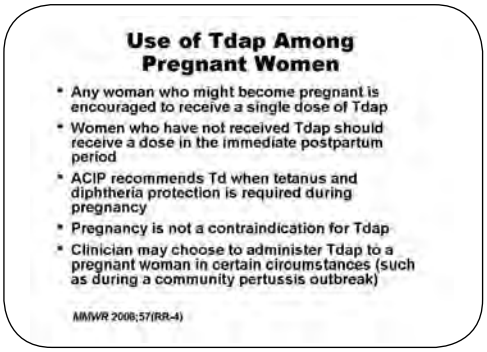
Vaccination of Pregnant Women

- Live vaccines should not be administered to women known to be pregnant
- In general inactivated vaccines may be administered to pregnant women for whom they are indicated
- HPV vaccine should be deferred during pregnancy

Since inactivated vaccines cannot replicate, they cannot cause fetal infection. In general, inactivated vaccines may be administered to pregnant women for whom they are indicated. An exception is human papillomavirus (HPV) vaccine, which should be deferred during pregnancy because of a lack of safety and efficacy data for this vaccine in pregnant women.

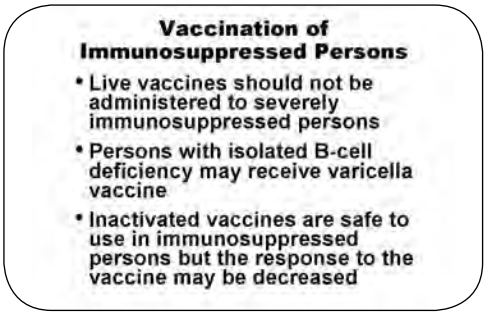
Pregnant women are at increased risk of complications of influenza. Any woman who will be pregnant during influenza season (generally December through March) should receive inactivated influenza vaccine. Pregnant women should not receive live attenuated influenza vaccine.

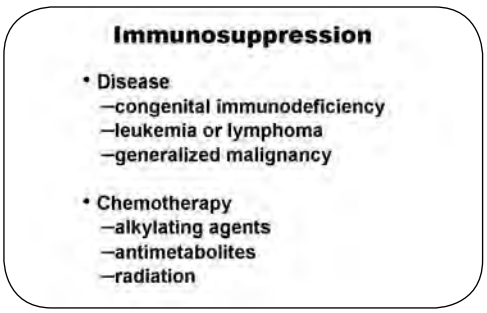
Any woman who might become pregnant is encouraged to receive a single dose of Tdap if she has not already received a dose. Women who have not received Tdap should receive a dose in the immediate postpartum period, before discharge from the hospital or birthing center.



ACIP recommends Td when tetanus and diphtheria protection is required during pregnancy. However, pregnancy is not a contraindication for use of Tdap. A clinician may choose to administer Tdap to a pregnant woman in certain circumstances, such as during a community pertussis outbreak. When Td or Tdap is administered during pregnancy, the second or third trimester is preferred to avoid coincidental association of vaccination and spontaneous termination of a pregnancy, which is more common in the first trimester. Clinicians can choose to administer Tdap instead of Td to protect against pertussis in pregnant adolescents for routine or "catch-up" vaccination because the incidence of pertussis is high among adolescents. They also may consider Tdap for pregnant healthcare personnel and child care providers to prevent transmission to infants younger than 12 months of age and other vulnerable persons, and for pregnant women employed in an institution or living in a community with increased pertussis activity.

Susceptible household contacts of pregnant women should receive MMR and varicella vaccines, and may receive LAIV, zoster and rotavirus vaccines if they are otherwise eligible.





Immunosuppression

Live vaccines can cause severe or fatal reactions in immunosuppressed persons due to uncontrolled replication of the vaccine virus. Live vaccines should not be administered to severely immunosuppressed persons for this reason. Persons with isolated B-cell deficiency may receive varicella vaccine. Inactivated vaccines cannot replicate, so they are safe to use in immunosuppressed persons. However, response to the vaccine may be decreased.

Both diseases and drugs can cause significant immunosuppression. Persons with congenital immunodeficiency, leukemia, lymphoma, or generalized malignancy should not receive live vaccines. However, MMR, varicella, rotavirus, and LAIV vaccines may be given when an immunosuppressed person lives in the same house. Household contacts of immunosuppressed persons may receive zoster vaccine if indicated. Transmission has not been documented from a person who received zoster vaccine.

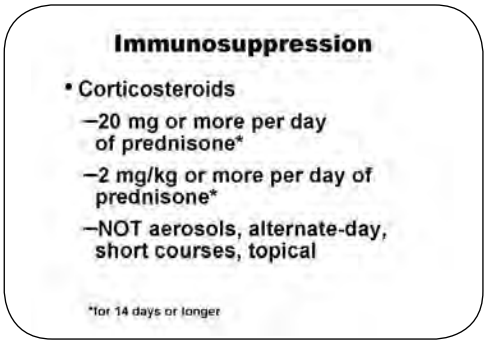
Certain drugs may cause immunosuppression. For instance, persons receiving cancer treatment with alkylating agents or antimetabolites, or radiation therapy should not be given live vaccines. Live vaccines can be given after chemotherapy has been discontinued for at least 3 months. Persons receiving large doses of corticosteroids should not receive live vaccines. For example, this would include persons receiving 20 milligrams or more of prednisone daily or 2 or more milligrams of prednisone per kilogram of body weight per day for 14 days or longer. See Chapter 20 for

more information about administration of zoster vaccine to immunosuppressed persons.

Aerosolized steroids, such as inhalers for asthma, are not contraindications to vaccination, nor are alternate-day, rapidly tapering, and short (less than 14 days) high-dose schedules, topical formulations, and physiologic replacement schedules.

The safety and efficacy of live attenuated vaccines administered concurrently with recombinant human immune mediators and immune modulators are not known. There is evidence that use of therapeutic monoclonal antibodies, especially the anti-tumor necrosis factor agents adalimumab, infliximab, and etanercept, may lead to reactivation of latent tuberculosis infection and tuberculosis disease and predispose to other opportunistic infections. Because the safety of live attenuated vaccines for persons receiving these drugs is not known, it is prudent to avoid administration of live attenuated vaccines for at least a month following treatment with these drugs.

Inactivated vaccines may be administered to immunosuppressed persons. Certain vaccines are recommended or encouraged specifically because immunosuppression is a risk factor for complications from vaccine-preventable diseases (i.e., influenza, invasive pneumococcal disease, invasive meningococcal disease, invasive *Haemophilus influenzae* type b disease, and hepatitis B). However, response to the vaccine may be poor depending on the degree of immunosuppression present. Because a relatively functional immune system is required to develop an immune response to a vaccine, an immunosuppressed person may not be protected even if the vaccine has been given. Additional recommendations for vaccination of immunosuppressed persons are detailed in the *General Recommendations on Immunization*.



HIV Infection

Persons infected with human immunodeficiency virus (HIV) may have no symptoms, or they may be severely immunosuppressed. In general, the same vaccination recommendations apply as with other types of immunosuppression. Live-virus vaccines are usually contraindicated, but inactivated vaccines may be administered if indicated.

Varicella and measles can be very severe illnesses in persons with HIV infection and are often associated with complications. Varicella vaccine is recommended for children (but not adults) with HIV infection who are not severely immunosuppressed. Zoster vaccine should not be given to persons with AIDS or clinical manifestations of HIV infection. Measles vaccine (as combination MMR vaccine) is recommended

Live Attenuated Vaccines for Persons with HIV/AIDS*

Vaccine	Asymptomatic	Symptomatic
Varicella	Yes	No
Zoster	No	No
MMR	Yes	No
MMRV	No	No
LAIV	No	No
Rotavirus	No	No
Yellow fever	Consider	No

Yes=vaccinate No=do not vaccinate

*see specific ACIP recommendations for details.

for persons with HIV infection who are asymptomatic or mildly immunosuppressed. However, persons with severe immunosuppression due to HIV infection should not receive measles vaccine or MMR. MMRV should not be administered to persons with HIV infection. Persons with HIV infection should not receive LAIV; they should receive inactivated influenza vaccine (TIV). Yellow fever vaccine should be considered for persons who do not have AIDS or other symptomatic manifestations of HIV infection, who have established laboratory verification of adequate immune system function, and who cannot avoid potential exposure to yellow fever virus.

Susceptible household contacts of persons with HIV infection should receive MMR and varicella vaccines, and may receive rotavirus, zoster and LAIV vaccines if otherwise eligible.

Vaccination of Hematopoietic Stem Cell Transplant Recipients

Hematopoietic stem cell transplant (HSCT) is the infusion of hematopoietic stem cells from a donor into a patient who has received chemotherapy and often radiation, both of which are usually bone marrow ablative. HSCT is used to treat a variety of neoplastic diseases, hematologic disorders, immunodeficiency syndromes, congenital enzyme deficiencies, and autoimmune disorders. HSCT recipients can receive either their own cells (i.e., autologous HSCT) or cells from a donor other than the transplant recipient (i.e., allogeneic HSCT).

Vaccination of Hematopoietic Stem Cell Transplant Recipients

- Antibody titers to VPDs decline during the 1-4 years after allogeneic or autologous HSCT if the recipient is not revaccinated
- HSCT recipients are at increased risk of some VPDs, particularly pneumococcal disease
- Revaccination recommended beginning 6-12 months posttransplant

MMWR 2000;49(RR-10)

Antibody titers to vaccine-preventable diseases (e.g., tetanus, poliovirus, measles, mumps, rubella, and encapsulated bacteria [i.e., *Streptococcus pneumoniae* and *Haemophilus influenzae* type b]) decline during the 1–4 years after allogeneic or autologous HSCT if the recipient is not revaccinated. HSCT recipients are at increased risk for certain vaccine-preventable diseases. As a result, HSCT recipients should be routinely revaccinated after HSCT, regardless of the source of the transplanted stem cells. Revaccination with inactivated vaccines should begin 12 months after HSCT. An exception to this recommendation is influenza vaccine, which should be administered 6 months after HSCT and annually thereafter for the life of the recipient. Revaccination with pneumococcal conjugate vaccine (PCV) can be considered, especially if the HSCT recipient is younger than 60 months. Two doses of PCV followed by a dose of pneumococcal polysaccharide vaccine (at least 8 weeks after the second dose of PCV) are recommended.

MMR and varicella vaccines should be administered 24 months after transplantation if the HSCT recipient is presumed to be immunocompetent. ACIP has not made a recommendation regarding the use of meningococcal and

Tdap vaccines among HSCT recipients. Use of these vaccines should be a case-by-case decision by the clinician.

Household and other close contacts of HSCT recipients and healthcare providers who care for HSCT recipients should be appropriately vaccinated, particularly against influenza, measles, and varicella. Additional details of vaccination of HSCT recipients and their contacts can be found in a CDC report on this topic available at http://www.cdc.gov/vaccines/pubs/textbks-manuals-guides.htm

Moderate or Severe Acute Illness

There is no evidence that a concurrent acute illness reduces vaccine efficacy or increases vaccine adverse events. The concern is that an adverse event (particularly fever) following vaccination could complicate the management of a severely ill person. If a person has a moderate or severe acute illness, vaccination with both live and inactivated vaccines should be delayed until the illness has improved.

Invalid Contraindications to Vaccination

Some healthcare providers inappropriately consider certain conditions or circumstances to be true contraindications or precautions to vaccinations. Such conditions or circumstances are known as invalid contraindications; they result in missed opportunities to administer needed vaccines. Some of the most common invalid contraindications are mild illnesses, conditions related to pregnancy and breastfeeding, allergies that are not anaphylactic in nature, and certain aspects of the patient's family history.

Invalid Contraindications to Vaccination

- Mild illness
- Antimicrobial therapy
- Disease exposure or convalescence
- Pregnant or immunosuppressed person in the household
- Breastfeeding
- Preterm birth
- Allergy to products not present in vaccine or allergy that is not anaphylactic
- Family history of adverse events
- Tuberculin skin test
- Multiple vaccines

Mild Illness

Children with mild acute illnesses, such as low-grade fever, upper respiratory infection (URI), colds, otitis media, and mild diarrhea, should be vaccinated on schedule. Several large studies have shown that young children with URI, otitis media, diarrhea, and/or fever respond to measles vaccine as well as those without these conditions. There is no evidence that mild diarrhea reduces the success of immunization of infants in the United States.

Low-grade fever is not a contraindication to immunization. Temperature measurement is not necessary before immunization if the infant or child does not appear ill and the parent does not say the child is currently ill. ACIP has not defined a body temperature above which vaccines should not be administered. The decision to vaccinate should be based on the overall evaluation of the person rather than an arbitrary body temperature.

Antimicrobial Therapy

Antibiotics do not have an effect on the immune response to most vaccines. The manufacturer advises that Ty21a oral typhoid vaccine should not be administered to persons receiving sulfonamides or other antibiotics; Ty21a should be administered at least 24 hours after a dose of an antibacterial drug.

No commonly used antimicrobial drug will inactivate a live-virus vaccine. However, antiviral drugs may affect vaccine replication in some circumstances. Live attenuated influenza vaccine should not be administered until 48 hours after cessation of therapy using antiviral drugs active against influenza (amantadine, rimantadine, zanamivir, oseltamivir). Antiviral drugs active against herpesviruses (acyclovir, famciclovir) should be discontinued 24 hours before administration of a varicella-containing vaccine, if possible.

Disease Exposure or Convalescence

If a person is not moderately or severely ill, he or she should be vaccinated. There is no evidence that either disease exposure or convalescence will affect the response to a vaccine or increase the likelihood of an adverse event.

Pregnant or Immunosuppressed Person in the Household

It is critical that healthy household contacts of pregnant women and immunosuppressed persons be vaccinated. Vaccination of healthy contacts reduces the chance of exposure of pregnant women and immunosuppressed persons.

Most vaccines, including live vaccines (MMR, varicella, zoster, rotavirus, LAIV, and yellow fever) can be administered to infants or children who are household contacts of pregnant or immunosuppressed persons, as well as to breastfeeding infants (where applicable). Vaccinia (smallpox) vaccine should not be administered to household contacts of a pregnant or immunosuppressed person in a nonemergency situation. Live attenuated influenza vaccine should not be administered to persons who have contact with severely immunosuppressed persons who are hospitalized and require care in a protected environment (i.e., who are in isolation because of immunosuppression). LAIV may be administered to contacts of persons with lesser degrees of immunosuppression.

Measles and mumps vaccine viruses produce a noncommunicable infection and are not transmitted to household contacts. Rubella vaccine virus has been shown to be shed in human milk, but transmission to an infant has rarely been documented. Transmission of varicella vaccine virus is not

common, and most women and older immunosuppressed persons are immune from having had chickenpox as a child. Transmission of zoster vaccine virus to household or other close contacts has not been reported.

Breastfeeding

Breastfeeding does not decrease the response to routine childhood vaccines and is not a contraindication for any vaccine except smallpox. Breastfeeding also does not extend or improve the passive immunity to vaccine-preventable disease that is provided by maternal antibody except possibly for *Haemophilus influenzae* type b. Breastfed infants should be vaccinated according to recommended schedules. Although rubella vaccine virus might be shed in human milk, infection of an infant is rare. LAIV may be administered to a woman who is breastfeeding if she is otherwise eligible; the risk of transmission of vaccine virus is unknown but is probably low.

Preterm Birth

Vaccines should be started on schedule on the basis of the child's chronological age. Preterm infants have been shown to respond adequately to vaccines used in infancy.

Studies demonstrate that decreased seroconversion rates might occur among preterm infants with very low birth weight (less than 2,000 grams) after administration of hepatitis B vaccine at birth. However, by 1 month chronological age, all preterm infants, regardless of initial birth weight or gestational age are as likely to respond as adequately as older and larger infants. All preterm infants born to hepatitis B surface antigen (HBsAg)-positive mothers and mothers with unknown HBsAg status must receive immunoprophylaxis with hepatitis B vaccine and hepatitis B immunoglobulin (HBIG) within 12 hours after birth. If these infants weigh less than 2,000 grams at birth, the initial vaccine dose should not be counted toward completion of the hepatitis B vaccine series, and three additional doses of hepatitis B vaccine should be administered beginning when the infant is 1 month of age.

Preterm infants with a birth weight of less than 2,000 grams who are born to women documented to be HBsAg-negative at the time of birth should receive the first dose of the hepatitis B vaccine series at 1 month of chronological age or at the time of hospital discharge.

Allergy to Products Not Present in Vaccine

Infants and children with nonspecific allergies, duck or feather allergy, or allergy to penicillin, children who have relatives with allergies, and children taking allergy shots

can and should be immunized. No vaccine available in the United States contains duck antigen or penicillin.

Allergy That is Not Anaphylactic

Anaphylactic allergy to a vaccine component (such as egg or neomycin) is a true contraindication to vaccination. If an allergy to a vaccine component is not anaphylactic, it is not a contraindication to that vaccine.

Family History of Adverse Events

The only family history that is relevant in the decision to vaccinate a child is immunosuppression. A family history of adverse reactions unrelated to immunosuppression or family history of seizures or sudden infant death syndrome (SIDS) is not a contraindication to vaccination. Varicella-containing vaccine (except zoster) should not be administered to persons who have a family history of congenital or hereditary immunodeficiency in first-degree relatives (e.g., parents and siblings) unless the immunocompetence of the potential vaccine recipient has been clinically substantiated or verified by a laboratory.

Tuberculin Skin Test

Infants and children who need a tuberculin skin test (TST) can and should be immunized. All vaccines, including MMR, can be given on the same day as a TST, or any time after a TST is applied. For most vaccines, there are no TST timing restrictions.

MMR vaccine may decrease the response to a TST, potentially causing a false-negative response in someone who actually has an infection with tuberculosis. MMR can be given the same day as a TST, but if MMR has been given and 1 or more days have elapsed, in most situations a wait of at least 4 weeks is recommended before giving a routine TST. No information on the effect of varicella-containing vaccine or LAIV on a TST is available. Until such information is available, it is prudent to apply rules for spacing measles vaccine and TST to varicella vaccine and LAIV.

Multiple Vaccines

As noted earlier in this chapter, administration at the same visit of all vaccines for which a person is eligible is critical to reaching and maintaining high vaccination coverage. All vaccines (except vaccinia) can be administered at the same visit as all other vaccines.

Screening for Contraindications and Precautions to Vaccination

The key to preventing serious adverse reactions is screening. Every person who administers vaccines should screen every patient for contraindications and precautions before giving the vaccine dose. Effective screening is not difficult or complicated and can be accomplished with just a few questions.

Is the child (or are you) sick today?

There is no evidence that acute illness reduces vaccine efficacy or increases vaccine adverse events. However, as a precaution, with moderate or severe acute illness, all vaccines should be delayed until the illness has improved. Mild illnesses (such as otitis media, upper respiratory infections, and diarrhea) are NOT contraindications to vaccination. Do not withhold vaccination if a person is taking antibiotics.

Does the child have allergies to medications, food, or any vaccine?

A history of anaphylactic reaction such as hives (urticaria), wheezing or difficulty breathing, or circulatory collapse or shock (not fainting) from a previous dose of vaccine or vaccine component is a contraindication for further doses. For example, if a person experiences anaphylaxis after eating eggs, do not administer influenza vaccine. It may be more efficient to inquire about allergies in a generic way (i.e., any food or medication) rather than to inquire about specific vaccine components. Most parents will not be familiar with minor components of vaccine, but they should know if the child has had an allergic reaction to a food or medication that was severe enough to require medical attention.

Has the child had a serious reaction to a vaccine in the past?

A history of anaphylactic reaction to a previous dose of vaccine or vaccine component is a contraindication for subsequent doses. A history of encephalopathy within 7 days following DTP/DTaP is a contraindication for further doses of pertussis-containing vaccine. Precautions to DTaP (not Tdap) include (a) seizure within 3 days of a dose, (b) pale or limp episode or collapse within 48 hours of a dose, (c) continuous crying for 3 hours within 48 hours of a dose, and (d) fever of 105°F (40°C) within 48 hours of a previous dose. There are other adverse events that might have occurred following vaccination that constitute contraindications or precautions to future doses. Usually vaccines are deferred when a precaution is present. However, situations may arise when the benefit outweighs the risk (e.g., during a community pertussis outbreak). A local reaction (redness or swelling at the site of injection) is not a contraindication to subsequent doses.

Screening Questions

- Is the child (or are you) sick today?
- Does the child have allergies to medications, food, or any vaccine?
- Has the child had a serious reaction to a vaccine in the past?
- Has the child had a seizure, or brain or nerve problem?
- Has the child had a health problem with asthma, lung disease, heart disease, kidney disease, metabolic disease such as diabetes, or a blood disorder?
- Does the child have cancer, leukemia, AIDS, or any other immune system problem?

Screening Questions

- Has the child taken cortisone, prednisone, other steroids, or anticancer drugs, or had x-ray treatments in the past 3 months?
- Has the child received a transfusion of blood or blood products, or been given a medicine called immune (gamma) globulin in the past year?
- Is the child/teen pregnant or is there a chance she could become pregnant during the next month?
- Has the child received vaccinations in the past 4 weeks?

Has the child had a seizure, or brain or nerve problem?

DTaP and Tdap are contraindicated for children who have a history of encephalopathy within 7 days following DTP/DTaP. An unstable progressive neurologic problem is a precaution to the use of DTaP and Tdap. For children with stable neurologic disorders (including seizures) unrelated to vaccination, or for children with a family history of seizure, vaccinate as usual but consider the use of acetaminophen or ibuprofen to minimize fever.

A history of Guillain-Barré syndrome is a precaution for tetanus-containing, influenza and meningococcal conjugate vaccines.

Has the child had a health problem with asthma, lung disease, heart disease, kidney disease, metabolic disease such as diabetes, or a blood disorder?

Children with any of these conditions should not receive LAIV. Children with these conditions should receive inactivated influenza vaccine only.

Does the child have cancer, leukemia, AIDS, or any other immune system problem?

Live-virus vaccines (e.g., MMR, varicella, rotavirus, and the intranasal live attenuated influenza vaccine [LAIV]) are usually contraindicated in immunocompromised children. However, there are exceptions. For example, MMR and varicella vaccines are recommended for asymptomatic HIV-infected children who do not have evidence of severe immunosuppression. Persons with severe immunosuppression should not receive MMR, varicella, rotavirus, or LAIV vaccines. For details, consult the ACIP recommendations for each vaccine.

Has the child taken cortisone, prednisone, other steroids, or anticancer drugs, or had x-ray treatments in the past 3 months?

Live-virus vaccines (e.g., MMR, varicella, zoster, LAIV) should be postponed until after chemotherapy or long-term, high-dose steroid therapy has ended. Details and the length of time to postpone vaccination are described elsewhere in this chapter and in the *General Recommendations on Immunization*.

Has the child received a transfusion of blood or blood products, or been given a medicine called immune (gamma) globulin in the past year?

Certain live virus vaccines (e.g., MMR and varicella) may need to be deferred, depending on the type of blood product and the interval since the blood product was administered. Information on recommended intervals between immune globulin or blood product administration and MMR or varicella vaccination is in Appendix A and in the *General Recommendations on Immunization*.

Is the child/teen pregnant or is there a chance she could become pregnant during the next month?

Live-virus vaccines (e.g., MMR, varicella, zoster, LAIV) are contraindicated during pregnancy because of the theoretical risk of virus transmission to the fetus. Sexually active young women who receive MMR or varicella vaccination should be instructed to practice careful contraception for 1 month following receipt of either vaccine. On theoretical grounds, inactivated poliovirus vaccine should not be given during pregnancy; however, it may be given if the risk of exposure is imminent (e.g., travel to endemic-disease areas) and immediate protection is needed. Use of Td or Tdap is not contraindicated in pregnancy. At the provider's discretion, either vaccine may be administered during the second or third trimester.

Has the child received vaccinations in the past 4 weeks?

If the child was given either live attenuated influenza vaccine or an injectable live-virus vaccine (e.g., MMR. varicella, yellow fever) in the past 4 weeks, he or she should wait 28 days before receiving another live vaccine. Inactivated vaccines may be given at the same time or at any time before or after a live vaccine.

Every person should be screened for contraindications and precautions before vaccination. Standardized screening forms for both children and adults have been developed by the Immunization Action Coalition and are available on their web site at http://www.immunize.org.

ACKNOWLEDGMENT

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Immunization Strategies for Healthcare Practices and Providers

The Need for Strategies to Increase Immunization Levels

An important component of an immunization provider practice is ensuring that the vaccines reach all children who need them. While attention to appropriate administration of vaccinations is essential, it cannot be assumed that these vaccinations are being given to every eligible child at the recommended age. Immunization levels in the Unites States are high, but gaps still exist, and providers can do much to maintain or increase immunization rates among patients in their practice. This chapter describes the need for increasing immunization levels and outlines strategies that providers can adopt to increase coverage in their own practice.

Vaccine-preventable disease rates in the United States are at very low levels. In 2007, only 43 cases of measles, 12 cases of rubella, no cases of diphtheria, 28 cases of tetanus, and no wild-type polio were reported to CDC. Given these immunization successes, one might question the continued interest in strategies to increase immunization levels.

However, although levels of vaccine-preventable diseases are low, this should not breed complacency regarding vaccination. For several reasons—including possible resurgence of disease, introduction of new vaccines, suboptimal immunization levels, cost-effectiveness, and gaps in sustainable immunization efforts—the need to focus on immunization rates remains crucial. The viruses and bacteria that cause vaccine-preventable disease and death still exist and can be passed on to unprotected persons or imported from other countries as demonstrated by measles outbreaks that occurred in 2008. Diseases such as measles, mumps, or pertussis can be more severe than often assumed and can result in social and economic as well as physical costs: sick children miss school, parents lose time from work, and illness among healthcare providers can severely disrupt a healthcare system. For many of these diseases, without vaccination, the incidence will rise to prevaccine levels.

Although levels of disease are the ultimate outcome of interest, these are a late indicator of the soundness of the immunization system. Immunization levels are a better indicator for determining if there is a problem with immunization delivery, and this chapter will focus on increasing immunization levels and the strategies healthcare providers can use to do this.

Specific concerns about U.S. immunization levels and areas for further study include the following:

Childhood immunization rates are still suboptimal. In 2007, for example, only 84.5% of children 19 to 35 months of age had received four doses of DTaP vaccine.

For other age groups, immunization rates are considerably lower than those for early childhood. According to Behavior Risk Factor Surveillance System data from 2005, a median of only 65.5% of persons 65 years of age and older received the influenza vaccine in the past 12 months, and 65.7% had ever received pneumococcal vaccine.

Economic and racial disparities exist. Low-income and minority children and adults are at greater risk for underimmunization. "Pockets of need" exist in our nation's inner cities.

Rates of influenza immunization are also unacceptably low among healthcare providers, an important target population for vaccination. Typically, fewer than 40% of healthcare providers receive influenza vaccine.

Why Focus on Strategies to Increase Immunization?

- Immunization levels not optimal
- Cost-effectiveness of some strategies uncertain
- Sustainable systems needed

Improvements in adult immunization rates have tapered off. According to data from the National Health Interview Survey, after a consistent increase in rates during the 1980s and early 1990s, improvements in influenza vaccination rates for adults 65 years of age and older have leveled off since 1997.

Cost-effectiveness needs more research. More research is needed regarding which strategies increase immunization levels with the least expenditure so these strategies can be prioritized.

Sustainable systems for vaccinating children, adolescents, and adults must be developed. High immunization rates cannot rest upon one-time or short-term efforts. Greater understanding of strategies to increase immunization levels is necessary in order to create lasting, effective immunization delivery systems.

Many strategies have been used to increase immunizations. Some, such as school entry laws, have effectively increased demand for vaccines, but the effectiveness of other strategies (e.g., advertising) is less well documented. Some proven strategies (e.g., reducing costs, linking immunization to Women Infants and Children (WIC) services, home visiting) are well suited to increasing rates among specific populations, such as persons with low access to immunization services.

One key to a successful strategy to increase immunization is matching the proposed solution to the current problem. At present in the United States, most persons have sufficient

interest in and access to health care and are seen, at least periodically, in healthcare systems. Those who remain unvaccinated are so largely because healthcare practices and providers do not always optimally perform the activities associated with delivering vaccines and keeping patients up-to-date with their immunization schedules. Although a combination of strategies—directed at both providers and the public—is necessary for increasing and maintaining high immunization rates, this chapter focuses on immunization strategies for healthcare practices and providers.

The AFIX Approach

The CDC, through state and other grantees, administers a program designed to move healthcare personnel from a state of unawareness about the problem of low immunization rates in their practice to one in which they are knowledgeable, concerned, motivated to change their immunization practices and capable of sustaining new behaviors. The acronym used for this approach is AFIX: Assessment of the immunization coverage of public and private providers, Feedback of diagnostic information to improve service delivery, Incentives to motivate providers to change immunization practices or recognition of improved or high performance, and eXchange of information among providers. First conceived by the Georgia Division of Public Health, AFIX is now being used nationwide with both public and private immunization providers and is recommended by governmental and nongovernmental vaccine programs and medical professional societies.

AFIX

Assessment
Feedback
Incentives
e**X**change

Overview

The AFIX process consists of an assessment of an immunization provider's coverage rates by a trained representative from the state or other immunization grantee program, feedback of the results of the assessment to provider staff, incentives to improve deficiencies and raise immunization rates, and exchange of information and ideas among healthcare providers. Some specific characteristics of this approach have made it one of the most effective for achieving high, sustainable vaccine coverage.

First, AFIX focuses on outcomes. It starts with an assessment, producing an estimate of immunization coverage levels in a provider's office, and these data help to identify specific actions to take in order to remedy deficiencies. Outcomes are easily measurable. Second, AFIX focuses on providers, those who are key to increasing immunization rates. AFIX requires no governmental policy changes, nor does it attempt to persuade clients to be vaccinated, but instead focuses on changing healthcare provider behavior. Third, AFIX, when used successfully, is a unique blend of advanced technology and personal interaction. Much of the AFIX

Special Characteristics of AFIX

- Focuses on outcomes
- Focuses on providers
- Blend of advanced technology and personal interaction

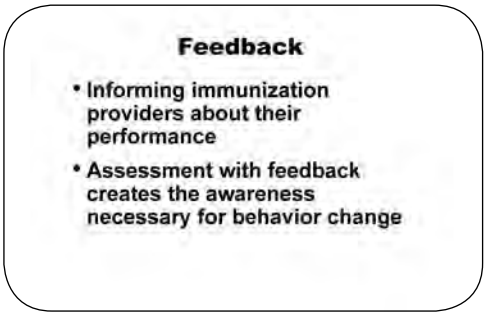
process can be done electronically, increasing speed and accuracy of assessment and feedback and streamlining reporting. However, the personal skills of the assessor and that person's ability to establish rapport with and motivate a provider are critical to achieving lasting results.

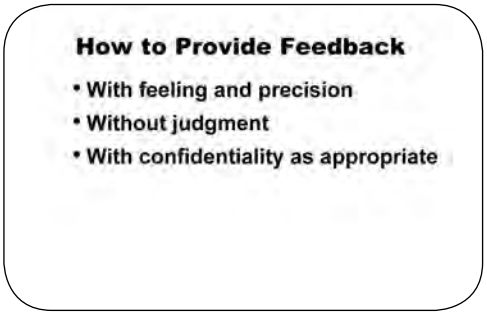


Assessment

Assessment refers to the evaluation of medical records to ascertain the immunization rate for a defined group of patients as well as to provide targeted diagnosis for improvement. This step is essential because several studies have documented that most healthcare providers, while supportive of immunizations, do not have an accurate perception of their own practice's immunization rates. Pediatricians in these studies greatly overestimated the proportion of fully immunized children in their practices. Assessment increases awareness of a provider's actual situation and provides a basis for subsequent actions by provider staff.

CDC has developed a software program, CoCASA, that enables assessment to be done electronically, is flexible enough to accommodate whatever assessment parameters are desired, and provides results that can be printed immediately. This program will be described further in the section, "AFIX Tools and Training."





Feedback

Feedback is the process of informing immunization providers about their performance in delivering one or more vaccines to a defined client population. The work of assessment is of no use unless the results are fed back to persons who can make a change. Assessment together with feedback creates the awareness necessary for behavior change.

Feedback generally consists of the immunization program representative meeting with appropriate provider staff and discussing the results of the assessment in order to determine the next steps to be taken. This may be done at a second visit following the assessment of the provider's records, or it may take place the same day. There are advantages and disadvantages to each approach. If CoCASA has been used, the summary report that is generated can identify specific subsets of patients (e.g., those who have not completed the series because of a missed opportunity for immunization) that, if found in substantial numbers, can provide clues to which changes in the provider's practice would be most effective. This can save time and make the feedback session more focused.

The personal element of feedback, as mentioned, is also critical to its success. A reviewer who is involved and

committed to the AFIX process, who addresses deficiencies without judgment, and who respects the confidentiality of the data and the efforts of the provider will be likely to gain the trust of providers and motivate them to increase immunization rates in the practice.

Incentives

An incentive is defined as something that incites one to action or effort. Incentives are built into the AFIX process, recognizing that immunization providers, like everyone else, will accomplish a desired task more successfully if motivated to do so. The assessment and feedback components are not intended to be done in isolation; providers may have sufficient data about their practice's immunization rates, but they must recognize high immunization coverage as a desirable goal and be motivated to achieve it.

Incentives

- Something that incites to action
- Vary by provider and stage of progress
- Opportunities for partnership and collaboration

Incentives are extremely variable. No one thing will be effective for every provider, and a single provider may need different types of motivation at different stages of progress. Things like small tokens of appreciation and providing resource materials at meetings have helped providers approach their task positively and create an atmosphere of teamwork, but longer-term goals must be considered as well. Since the effort to raise immunization rates may involve an increase in duties for staff, offering assistance in reviewing records or sending reminder notices might more directly address a provider's needs. Incentives pose a challenge to the creativity of the program representative but also offer the opportunity to try new ideas.

Finally, incentives are opportunities for partnerships and collaboration. Professional organizations or businesses have been solicited to publicize the immunization efforts in a newsletter or provide funding for other rewards for provider staff. Many other types of collaboration are possible; these also have the benefit of increasing awareness of immunization among diverse groups.

eXchange of Information

The final AFIX component, eXchange of information, goes hand in hand with incentives. The more information providers have about their own practice's immunization coverage status, how it compares with state norms and with other providers in their community, and what strategies have been successful with other providers, the more knowledgeable and motivated they will be to increase their immunization rates. It is up to the AFIX representative to provide appropriate statistical and educational information and create forums for exchange of information among providers.

eXchange of Information

- Allows access to more experience than an individual can accumulate
- Motivates improvement
- Coordinates resources and efforts

Staff members at all levels can benefit from the exchange of ideas about immunization practices and increasing rates of coverage—what has worked or not worked with another provider, streamlining office procedures, or where to obtain educational or other resources. The forums for such exchanges vary widely from informal meetings on the local level to more structured meetings sponsored by government or professional organizations. Immunization training sessions can be combined with sharing of ideas regarding actual situations in which recommendations, such as those from ACIP, are applied.

With the increased use of electronic communication, this method should not be neglected in the information exchange component of AFIX. Although different from face-to-face communication, e-mail exchanges or newsletters sent electronically can be cost-saving and fast means of disseminating information.

VFC/AFIX

- Incorporate AFIX activities during VFC site visits
- Combine VFC/AFIX site visits
- Reduces number of visits
- Extends reach of AFIX

VFC–AFIX Initiative

In the last several years, responsibility for immunization has largely shifted from public health departments to private providers, who now vaccinate nearly 80% of children in the United States. Many of these providers participate in the Vaccines for Children (VFC) program, a federal program whereby funding is provided for state and other immunization programs to purchase vaccines and make them available at no cost to children who meet income eligibility requirements. Because immunization program staff make periodic quality assurance site visits to VFC providers, CDC launched an initiative in 2000 to link some AFIX and VFC activities and incorporate AFIX activities during VFC provider site visits. VFC program staff are encouraged to promote the AFIX approach and, if possible, to combine VFC and AFIX site visits. This reduces the number of visits to a single provider and helps avoid duplication of staff time and effort. In addition, it increases the emphasis on overall quality improvement for a provider rather than meeting the requirements of a single program.

VFC serves more than 30,000 private provider sites, and every state participates in the program. VFC provider site visits are conducted to review compliance with VFC eligibility screening requirements and to evaluate vaccine storage and handling procedures. Linking VFC with AFIX enables AFIX to reach a large number of providers in the private sector and to reinforce the goals of both programs. Information about VFC can be found at http://www.cdc.gov/vaccines/programs/vfc/default.htm.

AFIX Tools And Training

The CDC has developed a software program titled Comprehensive Clinic Assessment Software Application (CoCASA) to enable electronic entry of AFIX and VFC site visit data. CoCASA, first released in December 2005, is an update of previous versions of CASA and supersedes previous versions. Using CoCASA, a reviewer enters appropriate basic information about an individual provider and conducts an assessment of patient records. The user also has the option to record AFIX visit outcomes and VFC site visit information.

CoCASA can provide immediate results of the assessment, supplying the reviewer with the information needed for use in the feedback session and noting areas that need further follow-up. CoCASA saves the reviewer time and provides various analysis options. CoCASA reports provide estimates of immunization coverage levels and potential reasons for the coverage level, such as missed opportunities for immunization and patients who did not return to finish the immunization series. The program can generate reports on specific sets of patients, such as those mentioned. Data from an immunization registry or patient management system can be imported into CoCASA, and data collected during the visit can be exported for further analysis.

CoCASA is available on the CDC Vaccines and Immunization website at http://www.cdc.gov/vaccines/programs/cocasa/default.htm. Comprehensive training modules on AFIX and on how to use CoCASA are built into the CoCASA program. Additional information about AFIX is available on the CDC Vaccines and Immunization website at http://www.cdc.gov/vaccines/programs/afix/default.htm.

Comprehensive Clinic Assessment Software Application (CoCASA)

- VFC and AFIX results
- Immediate assessment results
- Estimate of coverage levels
- Reasons for deficiencies
- Reports on patient subsets

AFIX Endorsements

AFIX is widely supported as an effective strategy to improve vaccination rates. Many states have shown gradual and consistent improvement in their coverage levels in the public sector, and studies of private pediatricians have also documented substantial improvements in median up-to-date coverage at 24 months. Assessment and feedback of public and private provider sites are recommended by the National Vaccine Advisory Committee (NVAC) in the Standards of Pediatric Immunization Practices as well as by the Advisory Committee on Immunization Practices (ACIP) in a statement endorsing the AFIX process and recommending its use by all public and private providers. *Healthy People 2010* also supports the AFIX concept with a recommendation for increasing the proportion of immunization providers who have measured vaccination levels among children in their practice within the past 2 years.

One of the Standards for Adult Immunization Practices issued by NVAC calls upon providers of adult immunization to do annual assessments of coverage levels. Although the use of AFIX among providers who serve adults is not as widespread as among childhood immunization providers, this strategy can be a powerful tool to improve rates in the adult population.

Other Essential Strategies

Although a substantial portion of this chapter is devoted to AFIX, certain other strategies for improvement of immunization levels deserve emphasis. These are complementary to AFIX; their adoption will support the goals of AFIX, i.e., raising immunization coverage levels, and will facilitate the AFIX process and ensure a favorable outcome of an assessment.

Strategies for High Immunization Levels

- Recordkeeping
- Recommendations and reinforcement
- Reminder and recall to patients
- Reminder and recall to providers
- Reduction of missed opportunities
- Reduction of barriers to immunization

Recordkeeping

Patient records are of vital importance in a medical practice, and maintaining these records, whether paper or electronic, is critical to providing optimal healthcare. Immunization records, specifically, should meet all applicable legal requirements as well as requirements of any specific program, such as VFC, in which the provider participates. These records should be available for inspection by an AFIX or VFC representative and should be easy to interpret by anyone examining the record.

Records

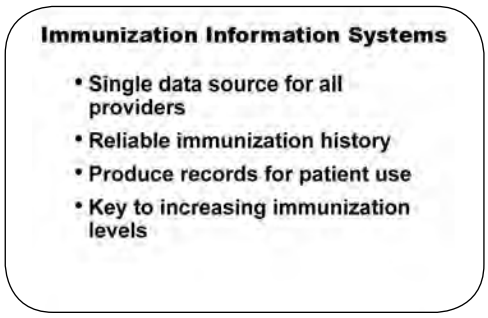
- Must be available at the time of the visit
- Must be easy to read
- Must be accurate
  - —reflect current patient population
  - —reflect all vaccines given

Immunization records must be accurate. The active medical records must reflect which patients are actually in the practice; charts of persons who have moved or are obtaining services elsewhere should be clearly marked accordingly or removed. Records should be kept up-to-date as new immunizations are administered, and all information regarding the vaccine and its administration should be complete.

Because patients often receive vaccines at more than one provider office, communication between sites is necessary for maintaining complete and accurate immunization records. School-based, public health, and community-based immunization sites should communicate with primary care personnel through quick and reliable methods such as, telephone, fax, or e-mail. This will become increasingly important as new vaccines for adolescents are added to the immunization schedule and more alternative sites are available for receiving immunizations.

Immunization Information Systems (IIS)

Many recordkeeping tasks, as well as patient reminder/recall activities, can be greatly simplified by participation in a population-based immunization information system (IIS), also known as an immunization registry. An IIS is a computerized information system that contains information about the immunization status of each child in a given geographic area (e.g., a state). In some areas, an IIS is linked to a child's complete medical record. An IIS provides a single data source for all community immunization providers, enabling access to records of children receiving vaccinations at multiple providers. It provides a reliable immunization history for every enrolled child and can also produce accurate immunization records, if needed for school or summer camp entry.



An IIS can also generate reminder/recall notices (discussed below), relieving provider staff of an additional burden, and can automatically produce reports of immunization coverage in an individual provider's practice, or by the child's age or geographic area. A goal of *Healthy People 2010* is to increase to 95% the proportion of children younger than 6 years of age who participate in fully operational, population-based immunization registries. In 2007, approximately 71% of children in this age-group met this participation goal. Federal, state and local public health agencies are continuing their efforts to improve the registries themselves and to increase participation by immunization providers. Registries are a key to increasing and maintaining immunization levels and provide benefits for providers, patients, and state and federal immunization program personnel. More information about immunization registries is available on the CDC Vaccines and Immunization website at http://www.cdc.gov/vaccines/programs/iis/default.htm.

Recommendations to Parents and Reinforcement of the Need to Return

The recommendation of a healthcare provider is a powerful motivator for patients to comply with vaccination recommendations. Parents of pediatric patients are likely to follow vaccine recommendation of the child's doctor, and even adults who were initially reluctant were likely to receive an influenza vaccination when the healthcare provider's opinion of the vaccine was positive.



Regardless of their child's true immunization status, many parents believe the child is fully vaccinated. Parents may not have been told or may not have understood that return visits are necessary. It is useful for patients to have the next appointment date in hand at the time they leave the provider's office. An additional reminder strategy is to link the timing of the return visit to some calendar event, e.g., the child's birthday or an upcoming holiday. Even with

written schedules or reminders, a verbal encouragement and reminder can be an incentive for a patient's completing the immunization series and can ultimately result in higher coverage levels.

Reminder and Recall to Patients

- Reminder—notification that immunizations are due soon
- Recall—notification that immunizations are past due
- Content of message and technique of delivery vary
- Reminders and recall have been found to be effective

Reminder and Recall Messages to Patients

Patient reminders and recall messages are messages to patients or their parents stating that recommended immunizations are due soon (reminders) or past due (recall messages). The messages vary in their level of personalization and specificity, the mode of communication, (e.g., postcard, letter, telephone), and the degree of automation. Both reminders and recall messages have been found to be effective in increasing attendance at clinics and improving vaccination rates in various settings.

Cost is sometimes thought to be a barrier to the implementation of a reminder/recall system. However, a range of options is available, from computer-generated telephone calls and letters to a card file box with weekly dividers, and these can be adapted to the needs of the provider. The specific type of system is not directly related to its effectiveness, and the benefits of having any system can extend beyond immunizations to other preventive services and increase the use of other recommended screenings.

Both the Standards for Child and Adolescent Immunization Practices and the Standards for Adult Immunization Practices call upon providers to develop and implement aggressive tracking systems that will both remind parents of upcoming immunizations and recall children who are overdue. ACIP supports the use of reminder/recall systems by all providers. The National Center for Immunization and Respiratory Diseases provides state and local health departments with ongoing technical support to assist them in implementing reminder and recall systems in public and private provider sites.

Reminder and Recall to Providers

- Communication to healthcare providers that an individual client's immunizations are due soon or past due
- Examples
  - —computer-generated list
  - —stamped note in the chart
  - —"Immunization Due" clip on chart

Reminder and Recall Messages to Providers

Providers can create reminder and recall systems for themselves as aids for remembering for which patients routine immunizations are due soon or past due. Provider reminder/recall is different from "feedback," in which the provider receives a message about overall immunization levels for a group of clients. Examples of reminder/recall messages are

- A computer-generated list that notifies a provider of the children to be seen that clinic session whose vaccinations are past due.

- A stamp with a message such as "No Pneumococcal Vaccine on Record," that a receptionist or nurse can put on a the chart of a person age 65 years or older.

- An "Immunization Due" clip that a nurse attaches to the chart of an adolescent who has not had hepatitis B vaccine.

Reminder systems will vary according to the needs of the provider; in addition to raising immunization rates in the practice, they will serve to heighten the awareness of staff members of the continual need to check the immunization status of their patients.

Reduction of Missed Opportunities to Vaccinate

A missed opportunity is a healthcare encounter in which a person is eligible to receive a vaccination but is not vaccinated completely. Missed opportunities occur in all settings in which immunizations are offered, whether routinely or not.

Missed Opportunity

A healthcare encounter in which a person is eligible to receive vaccination but is not vaccinated completely

Missed opportunities occur for several reasons. At the provider level, many nurses and physicians avoid simultaneous administration of four or even three injectable vaccines. Frequently stated reasons have included concern about reduced immune response or adverse events, and parental objection. These concerns are not supported by scientific data. Providers also may be unaware that a child is in need of vaccination (especially if the immunization record is not available at the visit) or may follow invalid contraindications (see Chapter 2 for more information).

Reasons for Missed Opportunities

- Lack of simultaneous administration
- Unaware child needs additional vaccines
- Invalid contraindications
- Inappropriate clinic policies
- Reimbursement deficiencies

Some of the reasons for missed opportunities relate to larger systems; e.g., a clinic that has a policy of not vaccinating at any visits except well-child care, or not vaccinating siblings. Other reasons relate to large institutional or bureaucratic regulations, such as state insurance laws that deny reimbursement if a vaccine is given during an acute-care visit. The degree of difficulty in eliminating the missed opportunity may vary directly with the size of the system that has to be changed.

Several studies have shown that eliminating missed opportunities could increase vaccination coverage by up to 20 percent. Strategies designed to prevent missed opportunities have taken many different forms, used alone or in combination. Examples include the following:

Strategies for Reducing Missed Opportunities

- Standing orders
- Provider education with feedback
- Provider reminder and recall systems

- Standing orders. These are protocols whereby nonphysician immunization personnel may vaccinate clients without direct physician involvement at the time of the immunization. Standing orders are implemented in settings such as clinics, hospitals, and nursing homes.

When used alone or in combination with other interventions, standing orders have had positive effects on immunization rates among adults.

- Provider education. Anyone responsible for administering immunizations should be knowledgeable about principles of vaccination and vaccination scheduling, to the extent required for their position. Providers are largely responsible for educating their patients, so an investment in provider education will result in a higher level of understanding about immunizations among the public in general. Numerous educational materials, in a variety of formats, are available from CDC, the Immunization Action Coalition, and some state health departments, hospitals, or professional organizations. Incorporating some AFIX principles (i.e., assessment, feedback) into a provider education program might have a greater effect on provider behavior than an education effort aimed only at increasing knowledge.

- Provider reminder and recall systems. Provider reminder and recall systems are discussed above. These reminder systems, while effective in increasing immunization levels, can also help avoid missed opportunities if they are a component of other practices directed toward this goal. For example, if a reminder system is used consistently and staff members are knowledgeable about vaccination opportunities and valid contraindications, the system can be an additional aid in promoting appropriate immunization practices.

Reduction of Barriers to Immunization Within the Practice

Reduction to Barriers to Immunization

- Physical barriers
  - –waiting time
  - –distance
- Psychological barriers
  - –unpleasant experience
  - –safety concerns

Despite efforts by providers to adhere to appropriate immunization practices, obstacles to patients' being vaccinated may exist within the practice setting, sometimes unknown to the provider. Barriers to immunization maybe physical or psychological. Physical barriers might be such things as inconvenient clinic hours for working patients or parents, long waits at the clinic, or the distance patients must travel. Providers should be encouraged to determine the needs of their specific patient population and take steps, such as extending clinic hours or providing some immunization clinics, to address obstacles to immunization.

Cost is also a barrier to immunization for many patients. In addition to evaluating their fee schedule for possible adjustments, providers should be knowledgeable about such programs as Vaccines for Children and the State Children's Health Insurance Program and the provisions specific to their state. Enrollment as a VFC provider is recommended for those with eligible children in their practice.

Psychological barriers to health care are often more subtle but may be just as important. Unpleasant experiences (e.g., fear of immunizations, being criticized for previously missed appointments, or difficulty leaving work for a clinic appointment) may lead clients to postpone receiving needed vaccinations. Concerns about vaccine safety are also preventing some parents from having their children immunized. Overcoming such barriers calls for both knowledge and interpersonal skills on the part of the provider—knowledge of vaccines and updated recommendations and of reliable sources to direct patients to find accurate information, and skills to deal with fears and misconceptions and to provide a supportive and encouraging environment for patients.

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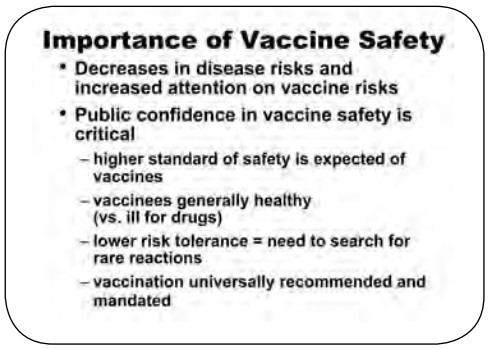
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Vaccine Safety

Vaccine safety is a prime concern for manufacturers, immunization providers, and recipients of vaccines. This chapter describes how vaccines licensed for use in the United States are monitored for safety, and presents general information about the provider's role in immunization safety. Further information about contraindications and precautions for individual vaccines, such as pregnancy and immunosuppression, and about potential adverse events associated with the vaccine is contained in Chapter 2, *General Recommendations on Immunization*, and in the chapters on specific vaccines.

The Importance of Vaccine Safety Programs

Vaccination is among the most significant public health success stories of all time. However, like any pharmaceutical product, no vaccine is completely safe or completely effective. While almost all known vaccine adverse events are minor and self-limited, some vaccines have been associated with very rare but serious health effects. The following key considerations underscore the need for an active and ongoing vaccine safety program.



Decreases in Disease Risks

Today, vaccine-preventable diseases are at or near record lows. By virtue of their absence, these diseases are no longer reminders of the benefits of vaccination. At the same time, approximately 15,000 cases of adverse events following vaccination are reported in the United States each year (these include both true adverse reactions and events that occur coincidentally after vaccination). This number exceeds the current reported incidence of vaccine-preventable childhood diseases. As a result, parents and providers in the United States are more likely to know someone who has experienced an adverse event following immunization than they are to know someone who has experienced a reportable vaccine-preventable disease. The success of vaccination has led to increased public attention on health risks associated with vaccines.

Public Confidence

Maintaining public confidence in immunizations is critical for preventing a decline in vaccination rates that can result in outbreaks of disease. While the majority of parents believe in the benefits of immunization and have their children vaccinated, some have concerns about the safety of vaccines. Public concerns about the safety of whole-cell pertussis vaccine in the 1980s resulted in decreased vaccine coverage levels and the return of epidemic disease in Japan,

Sweden, United Kingdom, and several other countries. In the United States, similar concerns led to increases both in the number of lawsuits against manufacturers and the price of vaccines, and to a decrease in the number of manufacturers willing to produce vaccines. Close monitoring and timely assessment of suspected vaccine adverse events can distinguish true vaccine reactions from coincidental unrelated events and help to maintain public confidence in immunizations.

A higher standard of safety is generally expected of vaccines than of other medical interventions because in contrast to most pharmaceutical products, which are administered to ill persons for curative purposes, vaccines are generally given to healthy persons to prevent disease. Public tolerance of adverse reactions related to products given to healthy persons, especially healthy infants and children, is substantially lower than for reactions to products administered to persons who are already sick. This lower risk tolerance of risk for vaccines translates into a need to investigate the possible causes of very rare adverse events following vaccinations.

Adding to public concern about vaccines is the fact that immunization is mandated by many state and local school entry requirements. Because of this widespread use, safety problems with vaccines can have a potential impact on large numbers of persons. The importance of ensuring the safety of a relatively universal human-directed "exposure" like immunizations is the basis for strict regulatory control of vaccines in the United States by the Food and Drug Administration (FDA).

Sound Immunization Recommendations and Policy

Public health recommendations for vaccine programs and practices represent a dynamic balancing of risks and benefits. Vaccine safety monitoring is necessary to accurately weigh this balance and adjust vaccination policy. This was done in the United States with smallpox and oral polio vaccines as these diseases neared global eradication. Complications associated with each vaccine exceeded the risks of the diseases, leading to discontinuation of routine smallpox vaccinations in the United States (prior to actual global eradication) and a shift to a safer inactivated polio vaccine. Sound immunization policies and recommendations affecting the health of the nation depend upon the ongoing monitoring of vaccines and continuous assessment of immunization benefits and risks.

Importance of Vaccine Safety

- Ongoing safety monitoring needed for the development of sound policies and recommendations

Methods of Monitoring Vaccine Safety

Prelicensure

Vaccines, like other pharmaceutical products, undergo extensive safety and efficacy evaluations in the laboratory, in animals, and in sequentially phased human clinical trials prior to licensure. Phase I human clinical trials usually involve anywhere from 20 to 100 volunteers and focus on detecting serious side effects. Phase II trials generally enroll hundreds of volunteers. These trials might take a few months, or last up to 3 years. Phase II trials determine the best dose for effectiveness and safety and the right number of doses. Next, the vaccine moves into phase III trials, which may last several years. A few hundred to several thousand volunteers may be involved. Some volunteers receive another already-licensed vaccine, allowing researchers to compare one vaccine with another for adverse health effects—anything from a sore arm to a serious reaction. If the vaccine is shown to be safe and effective in Phase III, the manufacturer applies for a license from the FDA. The FDA licenses the vaccine itself (the "product license") and licenses the manufacturing plant where the vaccine will be made (the "establishment license"). During the application, the FDA reviews everything: the clinical trial results, product labeling, the plant itself, and the manufacturing protocols.

FDA licensure occurs only after the vaccine has met rigorous standards of efficacy and safety, and when its potential benefits in preventing disease clearly outweigh any risks. However, while rates of common vaccine reactions, such as injection-site reactions and fever, can be estimated before licensure, the comparatively small number of patients enrolled in these trials generally limits detection of rare side effects or side effects that may occur many months after the vaccine is given. Even the largest prelicensure trials (more than 10,000 persons) are inadequate to assess the vaccine's potential to induce possible rare side effects. Therefore, it is essential to monitor reports of vaccine-associated adverse events once the vaccine has been licensed and released for public use.

Fundamental to preventing safety problems is the assurance that any vaccines for public use are made using Good Manufacturing Practices and undergo lot testing for purity and potency. Manufacturers must submit samples of each vaccine lot and results of their own tests for potency and purity to the FDA before releasing them for public use.

Prelicensure Vaccine Safety Studies

- Laboratory
- Animals
- Humans

Prelicensure Human Studies

- Phases I, II, III trials
- Common reactions are identified
- Vaccines are tested in thousands of persons before being licensed and allowed on the market

Postlicensure Surveillance

- Identify rare reactions
- Monitor increases in known reactions
- Identify risk factors for reactions
- Identify vaccine lots with unusual rates or types of events
- Identify signals

Postlicensure Vaccine Safety Activities

- Phase IV Trials
  - ~10,000 participants
  - better but still limited
- Large-Linked Databases
- Clinical Immunization Safety Assessment Network

Vaccine Adverse Event Reporting System (VAERS)

- National reporting system
- Jointly administered by CDC and FDA
- Passive (depends on healthcare providers and others to report)
- Receives ~15,000 reports per year

Vaccine Adverse Event Reporting System (VAERS)

- Detects
  - new or rare events
  - increases in rates of known side effects
  - patient risk factors
- Additional studies required to confirm VAERS signals
- Not all reports of adverse events are causally related to vaccine

Postlicensure

Because rare reactions, delayed reactions, or reactions within subpopulations may not be detected before vaccines are licensed, postlicensure evaluation of vaccine safety is critical. The objectives of postlicensure surveillance are to

- identify rare reactions not detected during prelicensure studies,
- monitor increases in known reactions,
- identify risk factors or preexisting conditions that may promote reactions,
- identify whether there are particular vaccine lots with unusually high rates or certain types of events,
- identify signals of possible adverse reactions that may warrant further study or affect current immunization recommendations.

Historically, postlicensure monitoring of vaccine safety has relied on healthcare providers and the public to report side effects, and on "ad hoc" research studies to investigate possible rare associations between vaccines and identified health conditions of interest to scientists. Today, Phase IV trials and large-linked databases (LLDBs) have been added to improve the capability to study rare risks of specific immunizations. Phase IV studies can be an FDA requirement for licensure. These trials include tens of thousands of volunteers and may address questions of long-term effectiveness and safety or examine unanswered questions identified in Phase III clinical trials. In 2001, a clinical immunization safety assessment network was established which will increase understanding of vaccine reactions at the individual patient level.

The Vaccine Adverse Event Reporting System

The National Childhood Vaccine Injury Act of 1986 mandated that healthcare providers who administer vaccines, and licensed vaccine manufactures, report certain adverse health events following specific vaccinations. The Vaccine Adverse Event Reporting System (VAERS) is a national reporting system, jointly administered by CDC and FDA. VAERS was created in 1990 to unify the collection of all reports of clinically significant adverse events. VAERS is a passive reporting system and accepts reports from health professionals, vaccine manufacturers, and the general public. Reports are submitted via mail and fax as well as the Internet. All reports, whether submitted directly to VAERS or via state or local public health authorities or manufacturers, are coded and entered into the VAERS database. VAERS receives about 15,000 reports per year (more than 200,000 total to date). Though this seems like a very large number, it is relatively small compared

with the approximately 100 million doses of childhood vaccines distributed during the past decade, as well as the millions of additional doses given to adults.

VAERS seeks to capture all clinically significant medical events occurring postvaccination, even if the reporter is not certain that the incident is vaccine related. A review of VAERS from 1991 through 2001 indicated that reports were received from manufacturers (36.2%), healthcare providers (20%), state and local health departments (27.6%), patients or parents (4.2%), others (7.3%), and unknown sources (4.7%).

Data collected on the VAERS reporting form include information about the patient, the vaccination(s) given, the reported health effect (called an adverse event—which may or may not be caused by vaccine), and the person reporting the event. Serious adverse event reports are defined as those involving hospitalization or prolongation of hospitalization, death, or reported life-threatening illness or permanent disability. All reports classified as serious are followed up to obtain additional medical information in order to provide as full a picture of the case as possible. For serious reports, letters to obtain information about recovery status are mailed to the reporters at 60 days and 1 year after vaccination. All records submitted to VAERS directly or as part of follow-up activities are protected by strict confidentiality requirements.

Despite some limitations, VAERS has been able to fulfill its primary purpose of detecting new or rare vaccine adverse events, increases in rates of known side effects, and patient risk factors for particular types of adverse events. Examples include tracking and raising the concern about intussusception after rotavirus vaccine and anaphylactic reaction to measles-mumps-rubella (MMR) vaccine caused by gelatin allergy. Additional studies are always required to confirm signals detected by VAERS because not all reported adverse events are causally related to vaccine. (See “Reporting Suspected Side Effects to VAERS” for detailed information on submitting reports.)

VAERS data with personal identifiers removed are available on the website at http://vaers.hhs.gov, at no cost or through the National Technical Information Service at http://www.ntis.gov or by phone at 800-553-6847 for a fee.

Adverse Event Classifications and Assessment of Causality

Adverse events following vaccination can be classified by frequency (common, rare), extent (local, systemic), severity (hospitalization, disability, death), causality, and preventability (intrinsic to vaccine, faulty production, faulty administration).

Adverse Event Classification

- Vaccine-induced
- Vaccine-potentiated
- Programmatic error
- Coincidental

Vaccine adverse events can be classified as follows:

- Vaccine-induced: Due to the intrinsic characteristic of the vaccine preparation and the individual response of the vaccinee. These events would not have occurred without vaccination (e.g., vaccine-associated paralytic poliomyelitis).
- Vaccine-potentiated: The event would have occurred anyway, but was precipitated by the vaccination (e.g., first febrile seizure in a predisposed child).
- Programmatic error: Due to technical errors in vaccine storage, preparation, handling, or administration.
- Coincidental: The reported event was not caused by vaccination but happened by chance occurrence or due to underlying illness.

It is natural to suspect a vaccine when a health problem occurs following vaccination, but in reality a causal association may or may not exist. More information would be needed to establish a causal relationship. An adverse health event can be causally attributed to vaccine more readily if 1) the health problem occurs during a plausible time period following vaccination, 2) the adverse event corresponds to those previously associated with a particular vaccine, 3) the event conforms to a specific clinical syndrome whose association with vaccination has strong biologic plausibility (e.g., anaphylaxis) or occurs following the natural disease, 4) a laboratory result confirms the association (e.g., isolation of vaccine strain varicella vaccine from skin lesions of a patient with rash), 5) the event recurs on re-administration of the vaccine ("positive rechallenge"), 6) a controlled clinical trial or epidemiologic study shows greater risk of a specific adverse event among vaccinated versus unvaccinated (control) groups, or 7) a finding linking an adverse event to vaccine has been confirmed by other studies.

Vaccine Safety Datalink (VSD)

In 1990, CDC established the Vaccine Safety Datalink (VSD) project to address gaps in the scientific knowledge of rare vaccine side effects. This project involves partnerships with eight large managed care organizations (MCOs) to monitor vaccine safety. MCOs' site locations as of April 2009 are Group Health Cooperative of Puget Sound, Seattle, Washington; Kaiser Permanente Northwest, Portland, Oregon; Kaiser Permanente Medical Care Program of Northern California, Oakland, California; Southern California Kaiser Permanente Health Care Program, Los Angeles, California; HealthPartners Research Foundation, Minneapolis, Minnesota; Marshfield Clinic Research Foundation, Marshfield, Wisconsin; Kaiser Permanente Colorado, Denver, Colorado; and Harvard Pilgrim Health Care, Boston, Massachusetts.

Each participating organization gathers data on vaccination (vaccine type, date of vaccination, concurrent vaccinations), medical outcomes (outpatient visits, inpatient visits, urgent care visits), birth data, and census data.

The VSD project allows for planned immunization safety studies as well as timely investigations of hypotheses that arise from review of medical literature, reports to the Vaccine Adverse Event Reporting System (VAERS), changes in immunization schedules, or the introduction of new vaccines.

In 2005, the Vaccine Safety Datalink (VSD) project team launched an active surveillance system called Rapid Cycle Analysis (RCA). Its goal is to monitor adverse events following vaccination in near real time, so the public can be informed quickly of possible risks. RCA data come from participating managed care organizations that include more than 8.8 million people annually, representing nearly 3% of the United States population. The RCA data contain no personal identifiers. The VSD project team is monitoring the safety of newly licensed vaccines, which includes conjugated meningococcal vaccine, rotavirus vaccines, MMRV vaccine, Tdap vaccine, Pentacel vaccine, Kinrix vaccine and HPV vaccine. In addition, the VSD RCA monitors the safety of seasonal influenza (flu) vaccinations. Further information about VSD is available at http://www.cdc.gov/vaccinesafety/vsd.

Vaccine Safety Datalink (VSD)

- Large-linked database
- Links vaccination and health records
- "Active surveillance"
  - –8 Managed Care Organizations
  - – ~3% of the U.S. population
- Powerful tool for monitoring vaccine safety

Clinical Immunization Safety Assessment Network

The most recent addition to the postlicensure vaccine safety monitoring system is the Clinical Immunization Safety Assessment (CISA) Network, which is designed to improve scientific understanding of vaccine safety issues at the individual patient level. The CISA network's goal is to evaluate persons who have experienced certain adverse health events following vaccination. The results of these evaluations will be used to gain a better understanding of how such events might occur and to develop protocols or guidelines for healthcare providers to help them manage similar situations. In addition, the CISA centers will serve as regional information sources to which clinical vaccine safety questions can be referred. Prior to the creation of the CISA network, no coordinated facilities in the United States investigated and managed vaccine side effects on an individual level for the purposes of providing patient care and systematically collecting and evaluating the experiences.

Clinical Immunization Safety Assessment (CISA) Network

- Improve understanding of vaccine safety issues at individual level
- Evaluate persons who experience adverse health events
- Gain better understanding of events
- Develop protocols for healthcare providers

Established in 2001, the CISA network consists of six centers of excellence with vaccine safety expertise working in partnership with CDC. These centers are Johns Hopkins University in Baltimore, Maryland; Boston University Medical Center in Boston, Massachusetts; Columbia Presbyterian Hospital in New York City; Vanderbilt University

in Nashville, Tennessee; Northern California Kaiser in Oakland, and Stanford University in Palo Alto, California. For more information about CISA, visit http://www.vaccinesafety.net.

Vaccine Injury Compensation

The topic of vaccine safety was prominent during the mid-1970s, with increases in lawsuits filed on behalf of those presumably injured by the whole-cell pertussis component of diphtheria-tetanus-pertussis (DPT) vaccine. Legal decisions were made and damages awarded despite the lack of scientific evidence to support vaccine injury claims. As a result of the liability, prices soared and several manufacturers halted vaccine production. A vaccine shortage resulted, and public health officials became concerned about the return of epidemic disease. To reduce liability and respond to public health concerns, Congress passed the National Childhood Vaccine Injury Act (NCVIA) in 1986.

Vaccine Injury Compensation Program (VICP)

- Established by National Childhood Vaccine Injury Act (1986)
- "No fault" program
- Covers all routinely recommended childhood vaccines
- Vaccine Injury Table

As a result of the NCVIA, the National Vaccine Injury Compensation Program (VICP) was established. This program is intended to compensate individuals who experience certain health events following vaccination on a "no fault" basis. "No fault" means that persons filing claims are not required to prove negligence on the part of either the healthcare provider or manufacturer to receive compensation. The program covers all routinely recommended childhood vaccinations. Settlements are based on a Vaccine Injury Table (Appendix F), which summarizes the adverse events associated with vaccines. This table was developed by a panel of experts who reviewed the medical literature and identified the serious adverse events that are reasonably certain to be caused by vaccines. The Vaccine Injury Table was created to justly compensate those possibly injured by vaccines while separating out unrelated claims. As more information becomes available from research on vaccine side effects, the Vaccine Injury Table is amended.

VICP has achieved its policy goals of providing compensation to those injured by rare adverse events and liability protection for vaccine manufacturers and administrators. Further information about the VICP is available at http://www.hrsa.gov/vaccinecompensation/

The Immunization Provider's Role

Even though federal regulations require vaccines to undergo years of testing before they can be licensed, and vaccines are monitored continually for safety and efficacy, immunization providers still play a key role in helping to ensure the safety and efficacy of vaccines. They do this through proper vaccine storage and administration, timing and spacing of vaccine doses, observation of precautions

The Provider's Role

- Immunization providers can help to ensure the safety and efficacy of vaccines through proper:
  - –vaccine storage and administration
  - –timing and spacing of vaccine doses
  - –observation of contraindications and precautions

and contraindications, management of vaccine side effects, reporting of suspected side effects to VAERS, and educating patients and parents about vaccine benefits and risks. Each of these steps is described only briefly here. Further information is available elsewhere in this book or in resource materials from CDC or other organizations.

Vaccine Storage and Administration

To achieve the best possible results from vaccines, immunization providers should carefully follow the recommendations found in each vaccine's package insert for storage, handling, and administration. Other steps to help ensure vaccine safety include 1) inspecting vaccines upon delivery and monitoring refrigerator and freezer temperatures to ensure maintenance of the cold chain, 2) rotating vaccine stock so the oldest vaccines are used first, 3) never administering a vaccine later than the expiration date, 4) administering vaccines within the prescribed time periods following reconstitution, 5) waiting to draw vaccines into syringes until immediately prior to administration, 6) never mixing vaccines in the same syringe unless they are specifically approved for mixing by the FDA, and 7) recording vaccine and administration information, including lot numbers and injection sites, in the patient's record. If errors in vaccine storage and administration occur, corrective action should be taken immediately to prevent them from happening again and public health authorities should be notified. More information on vaccine storage and handling is available in Appendix C and in CDC's Vaccine Storage and Handling Toolkit, available at http://www2a.cdc.gov/nip/isd/shtoolkit/splash.html

Timing and Spacing

Timing and spacing of vaccine doses are two of the most important issues in the appropriate use of vaccines. To ensure optimal results from each immunization, providers should follow the currently recommended immunization schedules for children, adolescents, and adults. Decreasing the timing intervals between doses of the same vaccine may interfere with the vaccine's antibody response. For more specific information on timing and spacing of vaccines see Chapter 2, *General Recommendations on Immunization*. A table showing recommended minimum ages and intervals between vaccine doses is contained in Appendix A.

Providers should also remember the following:

- Administering all needed vaccines during the same visit is important because it increases the likelihood that children will be fully immunized as recommended. Studies have shown that vaccines are as effective when administered simultaneously as they are individually and carry no greater risk for adverse reactions.

- There is no medical basis for giving combination vaccines, such as MMR, separately. Administration of separated combination vaccines results in more discomfort and higher risk of disease from delayed protection.
- Some vaccines, such as pediatric diphtheria and tetanus, produce increased rates of side effects when given too frequently. Good recordkeeping, maintaining careful patient histories, and adherence to recommended schedules can decrease the chances that patients receive extra doses of vaccines.

Contraindication

A condition in a recipient that increases the chance of a serious adverse reaction

Precaution

A condition in a recipient that might

- Increase the chance or severity of an adverse reaction, or
- Compromise the ability of the vaccine to produce immunity

Invalid Contraindications to Vaccination

- Minor illness
- Mild/moderate local reaction or fever following a prior dose
- Antimicrobial therapy
- Disease exposure or convalescence
- Pregnant or immunosuppressed in the household
- Premature birth
- Breastfeeding
- Allergies to products not in vaccine
- Family history (unrelated to immunosuppression)

Contraindications and Precautions

Contraindications and precautions to vaccination are conditions that indicate when vaccines should not be given. A contraindication is a condition in a recipient that increases the chance of a serious adverse reaction. In general, a vaccine should not be administered when a contraindication is present. A precaution is a condition in a recipient that might increase the chance or severity of an adverse reaction or compromise the ability of the vaccine to produce immunity. Normally, vaccination is deferred when a precaution is present. Situations may arise when the benefits of vaccination outweigh the risk of a side effect, and the provider may decide to vaccinate the patient. Most contraindications and precautions are temporary and the vaccine may be given at a later time. More information about contraindications can be found in the Advisory Committee on Immunization Practices (ACIP) statements for individual vaccines. Recommendations for immunizing persons who are immunocompromised can be found in Appendix A. Information on allergic reactions to vaccines can be found in the American Academy of Pediatrics *Red Book*.

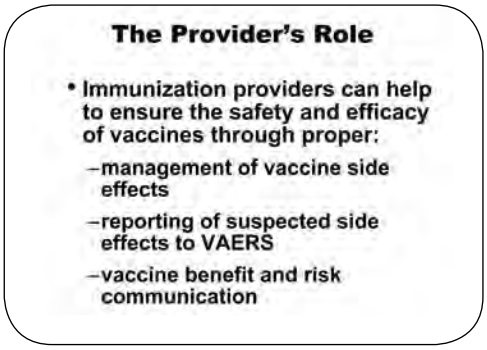
Screening for contraindications and precautions is key to preventing serious adverse reactions to vaccines. Every provider who administers vaccines should screen every patient before giving a vaccine dose. Sample screening questionnaires can be found in Chapter 2, *General Recommendations on Immunization*. Many conditions are often inappropriately regarded as contraindications to vaccination. In most cases, the following are not considered contraindications:

- Minor acute illness (e.g., diarrhea and minor upper respiratory tract illnesses, including otitis media) with or without low-grade fever
- Mild to moderate local reactions and/or low-grade or moderate fever following a prior dose of the vaccine
- Current antimicrobial therapy
- Recent exposure to infectious disease
- Convalescent phase of illness
- Pregnant or immunosuppressed person in the household

- Premature birth
- Breastfeeding
- Allergies to products not in vaccine
- Family history (unrelated to immunosuppression)

Managing Vaccine Side Effects

Providers should use their best clinical judgment regarding specific management of suspected vaccine side effects. Allergic reactions to vaccines are estimated to occur after vaccination of children and adolescents at a rate of one for every 1.5 million doses of vaccine. All providers who administer vaccines should have procedures in place and be prepared for emergency care of a person who experiences an anaphylactic reaction. Epinephrine and equipment for maintaining an airway should be available for immediate use. All vaccine providers should be familiar with the office emergency plan and should be certified in cardiopulmonary resuscitation.



Reporting Suspected Side Effects to VAERS

Healthcare providers are required by the National Childhood Vaccine Injury Act of 1986 to report certain events to VAERS and are encouraged to report any adverse event even if they are not sure a vaccine was the cause. A table listing reportable events is available at http://vaers.hhs.gov/reportable.htm. and is contained in Appendix F. Reporting can be done in one of three ways:

- Online through a secure website: https://secure.vaers.org/VaersDataEntryIntro.htm
- Fax a completed VAERS form* to 877-721-0366
- Mail a completed VAERS form* to

  VAERS
  P.O. Box 1100
  Rockville, MD 20849-1100

*A one-page VAERS form can be downloaded from http://vaers.hhs.gov/pdf/vaers_form.pdf or can be requested by telephone at 800-822-7967 or by fax at 877-721-0366. The form is also printed in Appendix F.

When providers report suspected vaccine reactions to VAERS, they provide valuable information that is needed for the ongoing evaluation of vaccine safety. CDC and FDA use VAERS information to ensure the safest strategies of vaccine use and to further reduce the rare risks associated with vaccines.

Benefit and Risk Communication

Parents, guardians, legal representatives, and adolescent and adult patients should be informed of the benefits and



risks of vaccines in understandable language. Opportunity for questions should be provided before each vaccination. Discussion of the benefits and risks of vaccination is sound medical practice and is required by law.

The National Childhood Vaccine Injury Act requires that vaccine information materials be developed for each vaccine covered by the Act. These materials, known as "Vaccine Information Statements (VISs)," must be provided by all public and private vaccination providers before each dose of vaccine. Copies of VISs are available from state health authorities responsible for immunization, or they can be obtained from CDC's website at http://www.cdc.gov/vaccines/pubs/vis/default.htm or from the Immunization Action Coalition at http://www.immunize.org. Translations of VISs into languages other than English are available from certain state immunization programs and from the Immunization Action Coalition website. Further information about VISs and their use is contained in Appendix E.

Healthcare providers should anticipate questions that parents or patients may have regarding the need for or safety of vaccination. A few may refuse certain vaccines, or even reject all vaccinations. Some persons might have religious or personal objections to vaccinations. Having a basic understanding of how patients view vaccine risk and developing effective approaches to dealing with vaccine safety concerns when they arise are imperative for vaccination providers. Healthcare providers can accomplish this by assessing patients' specific concerns and information needs, providing them with accurate information, and referring them to credible sources for more information. The CDC's website contains extensive and up-to-date information on vaccine safety issues http://www.cdc.gov/vaccines/.

When a parent or patient initiates discussion regarding a vaccine concern, the healthcare provider should discuss the specific concern and provide factual information, using language that is appropriate. Effective, empathetic vaccine risk communication is essential in responding to misinformation and concerns. The Vaccine Information Statements provide an outline for discussing vaccine benefits and risk. Other vaccine resources are available at http://www.cdc.gov/vaccinesafety/.

Rather than excluding from their practice those patients who question or refuse vaccination, the more effective public health strategy for providers is to identify common ground and discuss measures to be followed if the patient's decision is to defer vaccination. Healthcare providers can reinforce key points regarding each vaccine, including safety, and emphasize risks encountered by unimmunized children. Parents should be informed about state laws pertaining to school or child care entry, which might require that unim-

munized children stay home from school during outbreaks. Documentation of these discussions in the patient's record, including the refusal to receive certain vaccines (i.e., informed refusal), might reduce any potential liability if a vaccine-preventable disease occurs in the unimmunized patient.

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Diphtheria

Diphtheria is an acute, toxin-mediated disease caused by the bacterium *Corynebacterium diphtheriae*. The name of the disease is derived from the Greek *diphthera*, meaning leather hide. The disease was described in the 5th century BCE by Hippocrates, and epidemics were described in the 6th century AD by Aetius. The bacterium was first observed in diphtheritic membranes by Klebs in 1883 and cultivated by Löffler in 1884. Antitoxin was invented in the late 19th century, and toxoid was developed in the 1920s.

Diphtheria

- Greek *diphthera* (leather hide)
- Recognized by Hippocrates in 5th century BCE
- Epidemics described in 6th century
- *C. diphtheriae* described by Klebs in 1883
- Toxoid developed in 1920s

Corynebacterium diphtheriae

C. diphtheriae is an aerobic gram-positive bacillus. Toxin production (toxigenicity) occurs only when the bacillus is itself infected (lysogenized) by a specific virus (bacteriophage) carrying the genetic information for the toxin (tox gene). Only toxigenic strains can cause severe disease.

Culture of the organism requires selective media containing tellurite. If isolated, the organism must be distinguished in the laboratory from other *Corynebacterium* species that normally inhabit the nasopharynx and skin (e.g., diphtheroids).

C. diphtheriae has three biotypes—gravis, intermedius, and mitis. The most severe disease is associated with the gravis biotype, but any strain may produce toxin. All isolates of *C. diphtheriae* should be tested by the laboratory for toxigenicity.

Corynebacterium diphtheriae

- Aerobic gram-positive bacillus
- Toxin production occurs only when *C. diphtheriae* infected by virus (phage) carrying tox gene
- If isolated, must be distinguished from normal diphtheroid

Pathogenesis

Susceptible persons may acquire toxigenic diphtheria bacilli in the nasopharynx. The organism produces a toxin that inhibits cellular protein synthesis and is responsible for local tissue destruction and membrane formation. The toxin produced at the site of the membrane is absorbed into the bloodstream and then distributed to the tissues of the body. The toxin is responsible for the major complications of myocarditis and neuritis and can also cause low platelet counts (thrombocytopenia) and protein in the urine (proteinuria).

Clinical disease associated with non-toxin-producing strains is generally milder. While rare severe cases have been reported, these may actually have been caused by toxigenic strains that were not detected because of inadequate culture sampling.

Clinical Features

The incubation period of diphtheria is 2–5 days (range, 1–10 days).

Disease can involve almost any mucous membrane. For clinical purposes, it is convenient to classify diphtheria into a number of manifestations, depending on the site of disease.

Diphtheria Clinical Features

- Incubation period 2-5 days (range, 1-10 days)
- May involve any mucous membrane
- Classified based on site of infection
  - —anterior nasal
  - —pharyngeal and tonsillar
  - —laryngeal
  - —cutaneous
  - —ocular
  - —genital



Anterior Nasal Diphtheria

The onset of anterior nasal diphtheria is indistinguishable from that of the common cold and is usually characterized by a mucopurulent nasal discharge (containing both mucus and pus) which may become blood-tinged. A white membrane usually forms on the nasal septum. The disease is usually fairly mild because of apparent poor systemic absorption of toxin in this location, and it can be terminated rapidly by antitoxin and antibiotic therapy.

Pharyngeal and Tonsillar Diphtheria

The most common sites of diphtheria infection are the pharynx and the tonsils. Infection at these sites is usually associated with substantial systemic absorption of toxin. The onset of pharyngitis is insidious. Early symptoms include malaise, sore throat, anorexia, and low-grade fever. Within 2–3 days, a bluish-white membrane forms and extends, varying in size from covering a small patch on the tonsils to covering most of the soft palate. Often by the time a physician is contacted, the membrane is greyish-green, or black if bleeding has occurred. There is a minimal amount of mucosal erythema surrounding the membrane. The membrane is adherent to the tissue, and forcible attempts to remove it cause bleeding. Extensive membrane formation may result in respiratory obstruction.

The patient may recover at this point; or if enough toxin is absorbed, develop severe prostration, striking pallor, rapid pulse, stupor, and coma, and may even die within 6 to 10 days. Fever is usually not high, even though the patient may appear quite toxic. Patients with severe disease may develop marked edema of the submandibular areas and the anterior neck along with lymphadenopathy, giving a characteristic "bullneck" appearance.

Laryngeal Diphtheria

Laryngeal diphtheria can be either an extension of the pharyngeal form or can only involve this site. Symptoms include fever, hoarseness, and a barking cough. The membrane can lead to airway obstruction, coma, and death.

Cutaneous (Skin) Diphtheria

In the United States, cutaneous diphtheria has been most often associated with homeless persons. Skin infections are quite common in the tropics and are probably responsible for the high levels of natural immunity found in these populations. Skin infections may be manifested by a scaling rash or by ulcers with clearly demarcated edges and membrane, but any chronic skin lesion may harbor *C. diphtheriae* along with other organisms. Generally, the organisms isolated

from recent cases in the United States were nontoxigenic. The severity of the skin disease with toxigenic strains appears to be less than in other forms of infection with toxigenic strains. Skin diseases associated with nontoxigenic strains are no longer reported to the National Notifiable Diseases Surveillance System in the United States.

Other sites of involvement include the mucous membranes of the conjunctiva and vulvovaginal area, as well as the external auditory canal.

Complications

Most complications of diphtheria, including death, are attributable to effects of the toxin. The severity of the disease and complications are generally related to the extent of local disease. The toxin, when absorbed, affects organs and tissues distant from the site of invasion. The most frequent complications of diphtheria are myocarditis and neuritis.

Diphtheria Complications

- Most attributable to toxin
- Severity generally related to extent of local disease
- Most common complications are myocarditis and neuritis
- Death occurs in 5%-10%

Myocarditis may present as abnormal cardiac rhythms and can occur early in the course of the illness or weeks later, and can lead to heart failure. If myocarditis occurs early, it is often fatal.

Neuritis most often affects motor nerves and usually resolves completely. Paralysis of the soft palate is most frequent during the third week of illness. Paralysis of eye muscles, limbs, and diaphragm can occur after the fifth week. Secondary pneumonia and respiratory failure may result from diaphragmatic paralysis.

Other complications include otitis media and respiratory insufficiency due to airway obstruction, especially in infants.

Death

The overall case-fatality rate for diphtheria is 5%–10%, with higher death rates (up to 20%) among persons younger than 5 and older than 40 years of age. The case-fatality rate for diphtheria has changed very little during the last 50 years.

Laboratory Diagnosis

Diagnosis of diphtheria is usually made on the basis of clinical presentation since it is imperative to begin presumptive therapy quickly.

Culture of the lesion is done to confirm the diagnosis. It is critical to take a swab of the pharyngeal area, especially any discolored areas, ulcerations, and tonsillar crypts. Culture medium containing tellurite is preferred because it provides a selective advantage for the growth of this organism.

A blood agar plate is also inoculated for detection of hemolytic streptococcus. If diphtheria bacilli are isolated, they must be tested for toxin production.

Gram stain and Kenyon stain of material from the membrane itself can be helpful when trying to confirm the clinical diagnosis. The Gram stain may show multiple club-shaped forms that look like Chinese characters. Other *Corynebacterium* species (diphtheroids) that can normally inhabit the throat may confuse the interpretation of direct stain. However, treatment should be started if clinical diphtheria is suggested, even in the absence of a diagnostic Gram stain.

In the event that prior antibiotic therapy may have impeded a positive culture in a suspect diphtheria case, two sources of evidence can aid in presumptive diagnosis: 1) isolation of *C. diphtheriae* from cultures of specimens from close contacts, or 2) a low nonprotective diphtheria antibody titer (less than 0.1 IU) in serum obtained prior to antitoxin administration. This is done by commercial laboratories and requires several days. To isolate *C. diphtheriae* from carriers, it is best to inoculate a Löffler or Pai slant with the throat swab. After an incubation period of 18–24 hours, growth from the slant is used to inoculate a medium containing tellurite.

Medical Management

Diphtheria Antitoxin

Diphtheria antitoxin, produced in horses, was first used in the United States in 1891. It is no longer indicated for prophylaxis of contacts of diphtheria patients, only for the treatment of diphtheria. Since 1997, diphtheria antitoxin has been available only from CDC, and only through an Investigational New Drug (IND) protocol.

Diphtheria Antitoxin

- Produced in horses
- First used in the U.S. in 1891
- Used only for treatment of diphtheria
- Neutralizes only unbound toxin

Antitoxin will not neutralize toxin that is already fixed to tissues, but it will neutralize circulating (unbound) toxin and will prevent progression of disease. The patient must be tested for sensitivity before antitoxin is given. Consultation on the use of diphtheria antitoxin is available through the duty officer at the CDC during office hours (8:00 a.m.–4:30 p.m. ET) at 404-639-3158, or at all other times through CDC's Emergency Operations Center at 770-488-7100.

Persons with suspected diphtheria should be given antibiotics and antitoxin in adequate dosage and placed in isolation after the provisional clinical diagnosis is made and appropriate cultures are obtained. Respiratory support and airway maintenance should also be administered as needed.

Antibiotics

Treatment with erythromycin orally or by injection (40 mg/kg/day; maximum, 2 gm/day) for 14 days, or procaine penicillin G daily, intramuscularly (300,000 U/day for those weighing 10 kg or less, and 600,000 U/day for those weighing more than 10 kg) for 14 days. The disease is usually not contagious 48 hours after antibiotics are instituted. Elimination of the organism should be documented by two consecutive negative cultures after therapy is completed.

Preventive Measures

For close contacts, especially household contacts, a diphtheria booster, appropriate for age, should be given. Contacts should also receive antibiotics—benzathine penicillin G (600,000 units for persons younger than 6 years old and 1,200,000 units for those 6 years old and older) or a 7- to 10-day course of oral erythromycin, (40 mg/kg/day for children and 1 g/day for adults). For compliance reasons, if surveillance of contacts cannot be maintained, they should receive benzathine penicillin G. Identified carriers in the community should also receive antibiotics. Maintain close surveillance and begin antitoxin at the first signs of illness.

Contacts of cutaneous diphtheria should be treated as described above; however, if the strain is shown to be nontoxigenic, investigation of contacts can be discontinued.

Epidemiology

Occurrence

Diphtheria occurs worldwide, but clinical cases are more prevalent in temperate zones. In the United States during the pretoxoid era, the highest incidence was in the Southeast during the winter. More recently, highest incidence rates have been in states with significant populations of Native Americans. No geographic concentration of cases is currently observed in the United States.

Diphtheria Epidemiology

• Reservoir	Human carriers Usually asymptomatic
• Transmission	Respiratory Skin and fomites rarely
• Temporal pattern	Winter and spring
• Communicability	Up to several weeks without antibiotics

Reservoir

Human carriers are the reservoir for *C. diphtheriae* and are usually asymptomatic. In outbreaks, high percentages of children are found to be transient carriers.

Transmission

Transmission is most often person-to-person spread from the respiratory tract. Rarely, transmission may occur from skin lesions or articles soiled with discharges from lesions of infected persons (fomites).

Diphtheria

5

Temporal Pattern

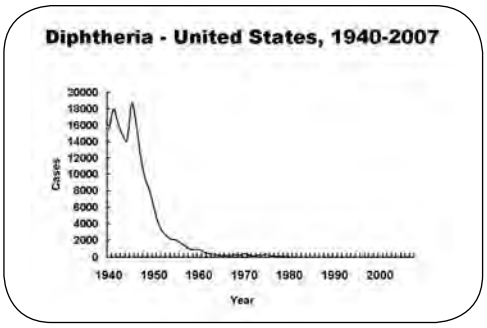
In temperate areas, diphtheria most frequently occurs during winter and spring.

Communicability

Transmission may occur as long as virulent bacilli are present in discharges and lesions. The time is variable, but organisms usually persist 2 weeks or less, and seldom more than 4 weeks, without antibiotics. Chronic carriers may shed organisms for 6 months or more. Effective antibiotic therapy promptly terminates shedding.

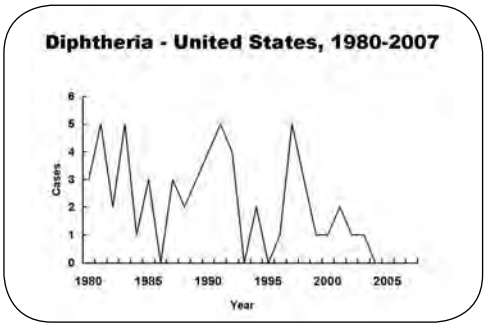
Secular Trends in the United States

Diphtheria was once a major cause of morbidity and mortality among children. In England and Wales during the 1930s, diphtheria was among the top three causes of death for children younger than 15 years of age.



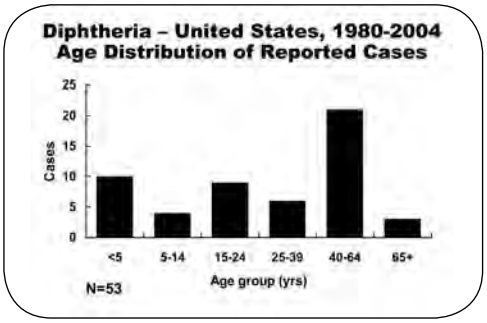
In the 1920s in the United States, 100,000–200,000 cases of diphtheria (140–150 cases per 100,000 population) and 13,000–15,000 deaths were reported each year. In 1921, a total of 206,000 cases and 15,520 deaths were reported. The number of cases gradually declined to about 19,000 cases in 1945 (15 per 100,000 population). A more rapid decrease began with the widespread use of toxoid in the late 1940s.

From 1970 to 1979, an average of 196 cases per year were reported. This included a high proportion of cutaneous cases from an outbreak in Washington State. Beginning in 1980, all cases with nontoxigenic cutaneous isolates were excluded from reporting. Diphtheria was seen most frequently in Native Americans and persons in lower socio-economic strata.



From 1980 through 2004, 57 cases of diphtheria were reported in the United States, an average of 2 or 3 per year (range, 0–5 cases per year). Only 5 cases have been reported since 2000.

Of 53 reported cases with known patient age since 1980, 31 (58%) were in persons 20 years of age or older; 44% of cases were among persons 40 years of age or older. Most cases have occurred in unimmunized or inadequately immunized persons. The current age distribution of cases corroborates the finding of inadequate levels of circulating antitoxin in many adults (up to 60% with less than protective levels).



Although diphtheria disease is rare in the United States, it appears that *Corynebacterium diphtheriae* continues to circulate in areas of the country with previously endemic diphtheria. In 1996, 10 isolates of *C. diphtheriae* were obtained from persons in an Native American community in South Dakota. Eight of these isolates were toxigenic.

None of the infected persons had classic diphtheria disease, although five had either pharyngitis or tonsillitis. The presence of toxigenic *C. diphtheriae* in this community is a good reminder for providers not to let down their guard against this organism.

Diphtheria continues to occur in other parts of the world. A major epidemic of diphtheria occurred in countries of the former Soviet Union beginning in 1990. By 1994, the epidemic had affected all 15 Newly Independent States (NIS). More than 157,000 cases and more than 5,000 deaths were reported. In the 6 years from 1990 through 1995, the NIS accounted for more than 90% of all diphtheria cases reported to the World Health Organization from the entire world. In some NIS countries, up to 80% of the epidemic diphtheria cases have been among adults. The outbreak and the age distribution of cases are believed to be due to several factors, including a lack of routine immunization of adults in these countries.

Diphtheria Toxoid

Characteristics

Beginning in the early 1900s, prophylaxis was attempted with toxin–antitoxin mixtures. Toxoid was developed around 1921 but was not widely used until the early 1930s. It was incorporated with tetanus toxoid and pertussis vaccine and became routinely used in the 1940s.

Diphtheria toxoid is produced by growing toxigenic *C. diphtheriae* in liquid medium. The filtrate is incubated with formaldehyde to convert toxin to toxoid and is then adsorbed onto an aluminum salt.

Single-antigen diphtheria toxoid is not available. Diphtheria toxoid is available combined with tetanus toxoid as pediatric diphtheria-tetanus toxoid (DT) or adult tetanus-diphtheria (Td), and with both tetanus toxoid and acellular pertussis vaccine as DTaP and Tdap. Diphtheria toxoid is also available as combined DTaP-HepB-IPV (Pediarix) and DTaP-IPV/Hib (Pentacel—see Chapter 14 for more information. Pediatric formulations (DT and DTaP) contain a similar amount of tetanus toxoid as adult Td, but contain 3 to 4 times as much diphtheria toxoid. Children younger than 7 years of age should receive either DTaP or pediatric DT. Persons 7 years of age or older should receive the adult formulation (adult Td), even if they have not completed a series of DTaP or pediatric DT. Two brands of Tdap are available—Boostrix (approved for persons 10 through 64 years of age) and Adacel (approved for persons 11 through 64 years of age). DTaP and Tdap vaccines do not contain thimerosal as a preservative.

DTaP, DT, Td and Tdap

	Diphtheria	Tetanus
DTaP, DT	7-8 Lf units	5-12.5 Lf units
Td, Tdap (adult)	2-2.5 Lf units	5 Lf units

DTaP and pediatric DT used through age 6 years. Adult Td for persons 7 years and older. Tdap for persons 10–64 years

Diphtheria Toxoid

- Formalin-inactivated diphtheria toxin
- Schedule — Three or four doses + booster
  Booster every 10 years
- Efficacy — Approximately 95%
- Duration — Approximately 10 years
- Should be administered with tetanus toxoid as DTaP, DT, Td, or Tdap

Routine DTaP Primary Vaccination Schedule

Dose	Age	Interval
Primary 1	2 months	---
Primary 2	4 months	4 weeks
Primary 3	6 months	4 weeks
Primary 4	15-18 months	6 months

Children Who Receive DT

- The number of doses of DT needed to complete the series depends on the child's age at the first dose:
  - –if first dose given at younger than 12 months of age, 4 doses are recommended
  - –if first dose given at 12 months or older, 3 doses complete the primary series

Routine DTaP Schedule for Children Younger Than 7 Years of Age

Booster Doses

- 4 through 6 years of age, before entering school
- 11 or 12 years of age if 5 years since last dose (Tdap)
- Every 10 years thereafter (Td)

Routine Td Schedule for Unvaccinated Persons 7 Years of Age and Older

Dose*	Interval
Primary 1	---
Primary 2	4 weeks
Primary 3	6 to 12 months

Booster dose every 10 years

*ACIP recommends that one of these doses (preferably the first) be administered as Tdap

Immunogenicity and Vaccine Efficacy

After a primary series of three properly spaced diphtheria toxoid doses in adults or four doses in infants, a protective level of antitoxin (defined as greater than 0.1 IU of antitoxin/mL) is reached in more than 95%. Diphtheria toxoid has been estimated to have a clinical efficacy of 97%.

Vaccination Schedule and Use

DTaP (diphtheria and tetanus toxoids and acellular pertussis vaccine) is the vaccine of choice for children 6 weeks through 6 years of age. The usual schedule is a primary series of 4 doses at 2,4,6, and 15–18 months of age. The first, second, and third doses of DTaP should be separated by a minimum of 4 weeks. The fourth dose should follow the third dose by no less than 6 months, and should not be administered before 12 months of age.

If a child has a valid contraindication to pertussis vaccine, pediatric DT should be used to complete the vaccination series. If the child was younger than 12 months old when the first dose of DT was administered (as DTP, DTaP, or DT), the child should receive a total of four primary DT doses. If the child was 12 months of age or older at the time the first dose of DT was administered, three doses (third dose 6–12 months after the second) completes the primary DT series.

If the fourth dose of DT, DTP or DTaP is administered before the fourth birthday, a booster (fifth) dose is recommended at 4 through 6 years of age. The fifth dose is not required if the fourth dose was given on or after the fourth birthday.

Because of waning antitoxin titers, most persons have antitoxin levels below the optimal level 10 years after the last dose. Tetanus toxoid should be given with diphtheria toxoid as Td every 10 years. The first booster dose may be given at 11 or 12 years of age if at least 5 years have elapsed since the last dose of DTP, DTaP, or DT. ACIP recommends this dose be administered as Tdap. If a dose is given sooner as part of wound management, the next booster is not needed for 10 years thereafter. More frequent boosters are not indicated and have been reported to result in an increased incidence and severity of local adverse reactions.

Td is the vaccine of choice for children 7 years and older and for adults. A primary series is three or four doses, depending on whether the person has received prior doses of diphtheria-containing vaccine and the age these doses were administered. The number of doses recommended for children who received one or more doses of DTP, DTaP, or DT before age 7 years is discussed above. For unvaccinated persons 7 years and older (including persons who cannot

document prior vaccination), the primary series is three doses. The first two doses should be separated by at least 4 weeks, and the third dose given 6 to 12 months after the second. For persons 10 years and older ACIP recommends that one of these doses (preferably the first) be administered as Tdap. A booster dose of Td should be given every 10 years. Tdap is approved for a single dose at this time (i.e., it should not be used for all the doses of Td in a previously unvaccinated person 7 years or older). Refer to the pertussis chapter for more information about Tdap.

Interruption of the recommended schedule or delay of subsequent doses does not reduce the response to the vaccine when the series is finally completed. There is no need to restart a series regardless of the time elapsed between doses.

Diphtheria disease might not confer immunity. Persons recovering from diphtheria should begin or complete active immunization with diphtheria toxoid during convalescence.

Contraindications and Precautions to Vaccination

Persons with a history of a severe allergic reaction (anaphylaxis) to a vaccine component or following a prior dose should not receive additional doses of diphtheria toxoid. Diphtheria toxoid should be deferred for those persons who have moderate or severe acute illness, but persons with minor illness may be vaccinated. Immunosuppression and pregnancy are not contraindications to receiving diphtheria toxoid. See pertussis chapter for additional information on contraindications and precautions to Tdap.

Diphtheria and Tetanus Toxoids Contraindications and Precautions

- Severe allergic reaction to vaccine component or following a prior dose
- Moderate or severe acute illness

Adverse Reactions Following Vaccination

Local reactions, generally erythema and induration with or without tenderness, are common after the administration of vaccines containing diphtheria toxoid. Local reactions are usually self-limited and require no therapy. A nodule may be palpable at the injection site for several weeks. Abscess at the site of injection has been reported. Fever and other systemic symptoms are not common.

Exaggerated local (Arthus-type) reactions are occasionally reported following receipt of a diphtheria- or tetanus-containing vaccine. These reactions present as extensive painful swelling, often from shoulder to elbow. They generally begin 2–8 hours after injections and are reported most often in adults, particularly those who have received frequent doses of diphtheria or tetanus toxoid. Persons experiencing these severe reactions usually have very high serum antitoxin levels; they should not be given

Diphtheria and Tetanus Toxoids Adverse Reactions

- Local reactions (erythema, induration)
- Fever and systemic symptoms not common
- Exaggerated local reactions (Arthus-type)
- Severe systemic reactions rare

further routine or emergency booster doses of Td more frequently than every 10 years. Less severe local reactions may occur in persons who have multiple prior boosters.

Rarely, severe systemic reactions such as generalized urticaria, anaphylaxis, or neurologic complications have been reported following administration of diphtheria toxoid.

Vaccine Storage and Handling

All diphtheria-toxoid-containing vaccines should be stored continuously at 35°–46°F (2°–8°C). Freezing reduces the potency of the tetanus component. Vaccine exposed to freezing temperature should never be administered.

Suspect Case Investigation and Control

Immediate action on all highly suspect cases (including cutaneous) is warranted until they are shown not to be caused by toxigenic *C. diphtheriae*. The following action should also be taken for any toxigenic *C. diphtheriae* carriers who are detected.

1. Contact state health department or CDC.

2. Obtain appropriate cultures and preliminary clinical and epidemiologic information (including vaccine history).

3. Begin early presumptive treatment with antibiotics and antitoxin. Impose strict isolation until at least two cultures are negative 24 hours after antibiotics were discontinued.

4. Identify close contacts, especially household members and other persons directly exposed to oral secretions of the patient. Culture all close contacts, regardless of their immunization status. Ideally, culture should be from both throat and nasal swabs. After culture, all contacts should receive antibiotic prophylaxis. Inadequately immunized contacts should receive DTaP/DT/Td/Tdap boosters. If fewer than three doses of diphtheria toxoid have been given, or vaccination history is unknown, an immediate dose of diphtheria toxoid should be given and the primary series completed according to the current schedule. If more than 5 years have elapsed since administration of diphtheria toxoid-containing vaccine, a booster dose should be given. If the most recent dose was within 5 years, no booster is required (see the ACIP's 1991 Diphtheria, Tetanus, and Pertussis: *Recommendations for Vaccine Use and Other Preventive Measures* for schedule for children younger than 7 years of age). Unimmunized contacts should start a course of DTaP/DT/Td vaccine and be monitored closely for symptoms of diphtheria for 7 days.

5. Treat any confirmed carrier with an adequate course of antibiotic, and repeat cultures at a minimum of 2 weeks

to ensure eradication of the organism. Persons who continue to harbor the organism after treatment with either penicillin or erythromycin should receive an additional 10-day course of erythromycin and should submit samples for follow-up cultures.

6. Treat any contact with antitoxin at the first sign of illness.

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Diphtheria

5

Haemophilus influenzae type b

Haemophilus influenzae is a cause of bacterial infections that are often severe, particularly among infants. It was first described by Pfeiffer in 1892. During an outbreak of influenza he found the bacteria in sputum of patients and proposed a causal association between this bacterium and the clinical syndrome known as influenza. The organism was given the name *Haemophilus* by Winslow, et al. in 1920. It was not until 1933 that Smith, et al. established that influenza was caused by a virus and that *H. influenzae* was a cause of secondary infection.

In the 1930s, Margaret Pittman demonstrated that *H. influenzae* could be isolated in encapsulated and unencapsulated forms. She identified six capsular types (a–f), and observed that virtually all isolates from cerebrospinal fluid (CSF) and blood were of the capsular type b.

Before the introduction of effective vaccines, *H. influenzae* type b (Hib) was the leading cause of bacterial meningitis and other invasive bacterial disease among children younger than 5 years of age; approximately one in 200 children in this age group developed invasive Hib disease. Nearly all Hib infections occurred among children younger than 5 years of age, and approximately two-thirds of all cases occurred among children younger than 18 months of age.

***Haemophilus influenzae* type b**

- Severe bacterial infection, particularly among infants
- During late 19th century believed to cause influenza
- Immunology and microbiology clarified in 1930s

Haemophilus influenzae

Haemophilus influenzae is a gram-negative coccobacillus. It is generally aerobic but can grow as a facultative anaerobe. In vitro growth requires accessory growth factors, including "X" factor (hemin) and "V" factor (nicotinamide adenine dinucleotide [NAD]).

Chocolate agar media are used for isolation. *H. influenzae* will generally not grow on blood agar, which lacks NAD.

The outermost structure of *H. influenzae* is composed of polyribosyl-ribitol phosphate (PRP), a polysaccharide that is responsible for virulence and immunity. Six antigenically and biochemically distinct capsular polysaccharide serotypes have been described; these are designated types a through f. In the prevaccine era, type b organisms accounted for 95% of all strains that caused invasive disease.

Haemophilus influenzae

- Aerobic gram-negative bacteria
- Polysaccharide capsule
- Six different serotypes (a-f) of polysaccharide capsule
- 95% of invasive disease caused by type b

Pathogenesis

The organism enters the body through the nasopharynx. Organisms colonize the nasopharynx and may remain only transiently or for several months in the absence of symptoms (asymptomatic carrier). In the prevaccine era, Hib could be

***Haemophilus influenzae* type b Pathogenesis**

- Organism colonizes nasopharynx
- In some persons organism invades bloodstream and causes infection at distant site
- Antecedent upper respiratory tract infection may be a contributing factor

isolated from the nasopharynx of 0.5%–3% of normal infants and children but was not common in adults. Nontypeable (unencapsulated) strains are also frequent inhabitants of the human respiratory tract.

In some persons, the organism causes an invasive infection. The exact mode of invasion to the bloodstream is unknown. Antecedent viral or mycoplasma infection of the upper respiratory tract may be a contributing factor. The bacteria spread in the bloodstream to distant sites in the body. Meninges are especially likely to be affected.

The most striking feature of Hib disease is age-dependent susceptibility. Hib disease is not common beyond 5 years of age. Passive protection of some infants is provided by transplacentally acquired maternal IgG antibodies and breastfeeding during the first 6 months of life. In the prevaccine era peak attack rates occurred at 6–7 months of age, declining thereafter. The presumed reason for this age distribution is the acquisition of immunity to Hib with increasing age.

Antibodies to Hib capsular polysaccharide are protective. The precise level of antibody required for protection against invasive disease is not clearly established. However, a titer of 1 μg/mL 3 weeks postvaccination correlated with protection in studies following vaccination with unconjugated purified polyribosylribitol phosphate (PRP) vaccine and suggested long-term protection from invasive disease.

Acquisition of both anticapsular and serum bactericidal antibody is inversely related to the age-specific incidence of Hib disease.

In the prevaccine era, most children acquired immunity by 5–6 years of age through asymptomatic infection by Hib bacteria. Since only a relatively small proportion of children carry Hib at any time, it has been postulated that exposure to organisms that share common antigenic structures with the capsule of Hib (so-called "cross-reacting organisms") may also stimulate the development of anticapsular antibodies against Hib. Natural exposure to Hib also induces antibodies to outer membrane proteins, lipopolysaccharides, and other antigens on the surface of the bacterium.

The genetic constitution of the host may also be important in susceptibility to infection with Hib. Risk for Hib disease has been associated with a number of genetic markers, but the mechanism of these associations is unknown. No single genetic relationship regulating susceptibility or immune responses to polysaccharide antigens has yet been convincingly demonstrated.

Clinical Features

Invasive disease caused by *H. influenzae* type b can affect many organ systems. The most common types of invasive disease are meningitis, epiglottitis, pneumonia, arthritis, and cellulitis.

Meningitis is infection of the membranes covering the brain and is the most common clinical manifestation of invasive Hib disease, accounting for 50%–65% of cases in the prevaccine era. Hallmarks of Hib meningitis are fever, decreased mental status, and stiff neck (these symptoms also occur with meningitis caused by other bacteria). Hearing impairment or other neurologic sequelae occur in 15%–30% of survivors. The case-fatality rate is 2%–5%, despite appropriate antimicrobial therapy.

Epiglottitis is an infection and swelling of the epiglottis, the tissue in the throat that covers and protects the larynx during swallowing. Epiglottitis may cause life-threatening airway obstruction.

Septic arthritis (joint infection), cellulitis (rapidly progressing skin infection which usually involves face, head, or neck), and pneumonia (which can be mild focal or severe empyema) are common manifestations of invasive disease.

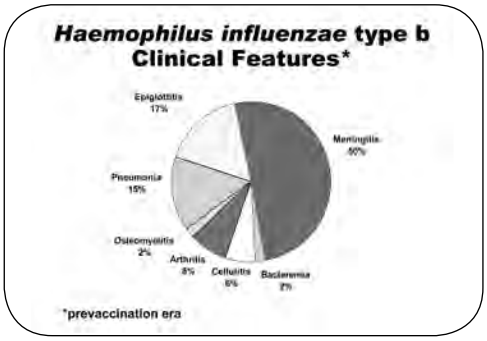
Osteomyelitis (bone infection) and pericarditis (infection of the sac covering the heart) are less common forms of invasive disease. Otitis media and acute bronchitis due to *H. influenzae* are generally caused by nontypeable strains. Hib strains account for only 5%–10% of *H. influenzae* causing otitis media.

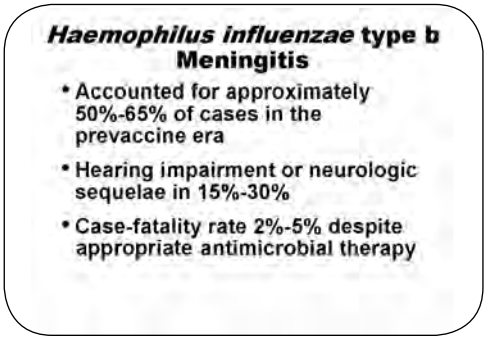
Nontypeable (unencapsulated) strains may cause invasive disease but are generally less virulent than encapsulated strains. Nontypeable strains are rare causes of serious infection among children but are a common cause of ear infections in children and bronchitis in adults.

Laboratory Diagnosis

A Gram stain of an infected body fluid may demonstrate small gram-negative coccobacilli suggestive of invasive *Haemophilus* disease. CSF, blood, pleural fluid, joint fluid, and middle ear aspirates should be cultured on appropriate media. A positive culture for *H. influenzae* establishes the diagnosis.

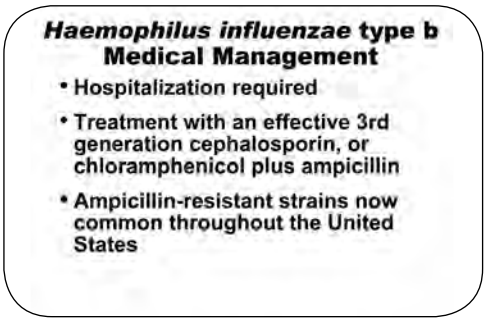
All isolates of *H. influenzae* should be serotyped. This is an extremely important laboratory procedure that should be performed on every isolate of *H. influenzae*, especially those obtained from children younger than 15 years of age. This test determines whether an isolate is type b, which is the only type that is potentially vaccine preventable. Serotyping





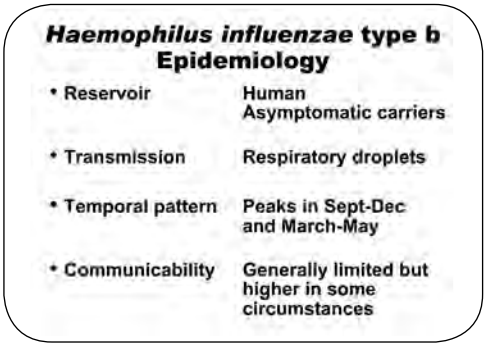
is usually done by either the state health department laboratory or a reference laboratory.

Antigen detection may be used as an adjunct to culture, particularly in diagnosing *H. influenzae* infection in patients who have been partially treated with antimicrobial agents, in which case the organism may not be viable on culture. Two tests are available. Latex agglutination is a rapid, sensitive, and specific method to detect Hib capsular polysaccharide antigen in CSF, but a negative test does not exclude the diagnosis, and false-positive tests have been reported. Antigen testing of serum and urine is not recommended. Counterimmunoelectrophoresis is similar to latex agglutination but is less sensitive, takes longer, and is more difficult to perform.



Medical Management

Hospitalization is generally required for invasive Hib disease. Antimicrobial therapy with an effective third-generation cephalosporin (cefotaxime or ceftriaxone), or chloramphenicol in combination with ampicillin should be begun immediately. The treatment course is usually 10 days. Ampicillin-resistant strains of Hib are now common throughout the United States. Children with life-threatening illness in which Hib may be the etiologic agent should not receive ampicillin alone as initial empiric therapy.



Epidemiology

Occurrence

Hib disease occurs worldwide.

Reservoir

Humans (asymptomatic carriers) are the only known reservoir. Hib does not survive in the environment on inanimate surfaces.

Transmission

The primary mode of Hib transmission is presumably by respiratory droplet spread, although firm evidence for this mechanism is lacking.

Temporal Pattern

Several studies in the prevaccine era described a bimodal seasonal pattern in the United States, with one peak during September through December and a second peak during March through May. The reason for this bimodal pattern is not known.

Communicability

The contagious potential of invasive Hib disease is considered to be limited. However, certain circumstances, particularly close contact with a case-patient (e.g., household, child care, or institutional setting) can lead to outbreaks or direct secondary transmission of the disease.

Secular Trends in the United States

H. influenzae infections became nationally reportable in 1991. Serotype-specific reporting continues to be incomplete.

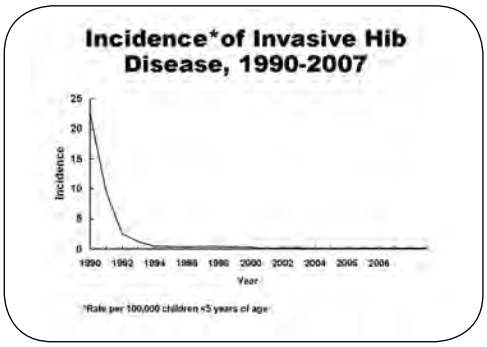
Before the availability of national reporting data, several areas conducted active surveillance for *H. influenzae* disease, which allowed estimates of disease nationwide. In the early 1980s, it was estimated that about 20,000 cases occurred annually in the United States, primarily among children younger than 5 years of age (40–50 cases per 100,000 population). The incidence of invasive Hib disease began to decline dramatically in the late 1980s, coincident with licensure of conjugate Hib vaccines, and has declined by more than 99% compared with the prevaccine era.

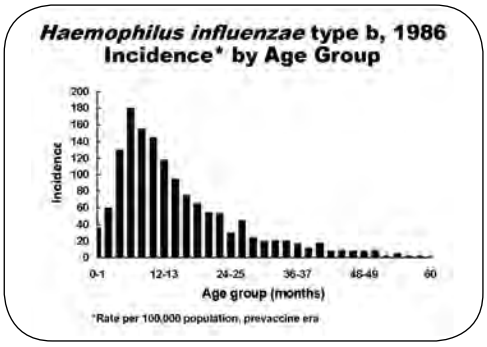
From 1996 through 2000, an average of 1,247 invasive *H. influenzae* infections per year were reported to CDC in all age groups (range 1,162–1,398 per year). Of these, an average of 272 (approximately 22%) per year were among children younger than 5 years of age. Serotype was known for 76% of the invasive cases in this age group. Three-hundred forty-one (average of 68 cases per year) were due to type b.

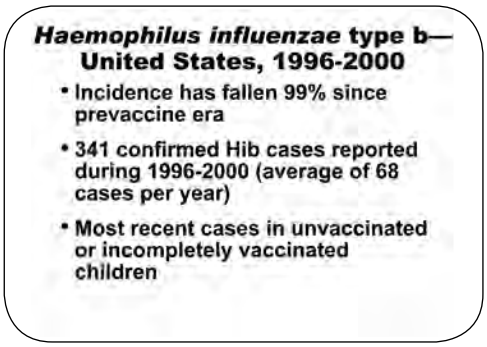
There is evidence that Hib vaccines decrease the rate of carriage of Hib among vaccinated children, thereby decreasing the chance that unvaccinated children will be exposed.

Incidence is strikingly age-dependent. In the prevaccine era, up to 60% of invasive disease occurred before age 12 months, with a peak occurrence among children 6–11 months of age. Children 60 months of age and older account for less than 10% of invasive disease.

In 1998–2000, approximately 44% of children younger than 5 years of age with confirmed invasive Hib disease were younger than 6 months of age and too young to have completed a three-dose primary vaccination series. Fifty-six percent were age 6 months or older and were eligible to have completed the primary vaccination series. Of these age-eligible children, 68% were either incompletely vaccinated (fewer than 3 doses) or their vaccination status was unknown. Thirty-two percent of children aged 6–59 months with confirmed type b disease had received three or more doses of Hib vaccine, including 22 who had received a booster dose 14 or more days before onset of their illness. The cause of Hib vaccine failure in these children is not known.







Haemophilus influenzae type b

Haemophilus influenzae type b
Risk Factors for Invasive Disease

- Exposure factors
  - household crowding
  - large household size
  - child care attendance
  - low socioeconomic status
  - low parental education
  - school-aged siblings
- Host factors
  - race/ethnicity
  - chronic disease

In 2007, among children younger than 5 years of age, 22 cases of invasive disease due to Hib were reported in the United States. In addition, another 180 cases caused by unknown *H. influenzae* serotypes were reported, so the actual number of Hib cases could be between 22 and 202. Most cases were among unvaccinated or incompletely vaccinated children.

Risk factors for Hib disease include exposure factors and host factors that increase the likelihood of exposure to Hib. Exposure factors include household crowding, large household size, child care attendance, low socioeconomic status, low parental education levels, and school-aged siblings. Host factors include race/ethnicity (elevated risk among African Americans, Hispanics, Native Americans—possibly confounded by socioeconomic variables that are associated with both race/ethnicity and Hib disease), chronic disease (e.g., sickle cell anemia, antibody deficiency syndromes, malignancies, especially during chemotherapy), and possibly gender (risk is higher for males).

Protective factors (effect limited to infants younger than 6 months of age) include breastfeeding and passively acquired maternal antibody.

Secondary Hib disease is defined as illness occurring 1–60 days following contact with an ill child, and accounts for less than 5% of all invasive Hib disease. Among household contacts, six studies have found a secondary attack rate of 0.3% in the month following onset of the index case, which is about 600-fold higher than the risk for the general population. Attack rates varied substantially with age, from 3.7% among children 2 years of age and younger to 0% among contacts 6 years of age and older. In these household contacts, 64% of secondary cases occurred within the first week (excluding the first 24 hours) of disease onset in the index patient, 20% during the second week, and 16% during the third and fourth weeks.

Data are conflicting regarding the risk of secondary transmission among child care contacts. Secondary attack rates have varied from 0% to as high as 2.7%. Most studies seem to suggest that child care contacts are at relatively low risk for secondary transmission of Hib disease particularly if contacts are age-appropriately vaccinated.

Haemophilus influenzae type b
Polysaccharide Vaccine

- Available 1985-1988
- Not effective in children younger than 18 months of age
- Effectiveness in older children variable

Haemophilus influenzae type b Vaccines

Characteristics

A pure polysaccharide vaccine (HbPV) was licensed in the United States in 1985. The vaccine was not effective in children younger than 18 months of age. Estimates of efficacy in older children varied widely, from 88% to -69% (a negative efficacy implies greater disease risk for vaccinees

than nonvaccinees). HbPV was used until 1988 but is no longer available in the United States.

The characteristics of the Hib polysaccharide were similar to other polysaccharide vaccines (e.g., pneumococcal, meningococcal). The response to the vaccine was typical of a T-independent antigen, most notably an age-dependent immune response, and poor immunogenicity in children 2 years of age and younger. In addition, no boost in antibody titer was observed with repeated doses, the antibody that was produced was relatively low-affinity IgM, and switching to IgG production was minimal.

Polysaccharide Vaccines

- Age-related immune response
- Not consistently immunogenic in children 2 years of age and younger
- No booster response
- Antibody with less functional activity

Haemophilus influenzae type b Polysaccharide-Protein Conjugate Vaccines

Conjugation is the process of chemically bonding a polysaccharide (a somewhat ineffective antigen) to a protein "carrier," which is a more effective antigen. This process changes the polysaccharide from a T-independent to a T-dependent antigen and greatly improves immunogenicity, particularly in young children. In addition, repeat doses of Hib conjugate vaccines elicit booster responses and allow maturation of class-specific immunity with predominance of IgG antibody. The Hib conjugates also cause carrier priming and elicit antibody to "useful" carrier protein.

Polysaccharide Conjugate Vaccines

- Stimulates T-dependent immunity
- Enhanced antibody production, especially in young children
- Repeat doses elicit booster response

The first Hib conjugate vaccine (PRP-D, ProHIBIT) was licensed in December 1987. PRP-D is no longer available in the United States. HibTITER (HbOC) is no longer available.

Two conjugate Hib vaccines are licensed for use in infants as young as 6 weeks of age (see below). The vaccines utilize different carrier proteins. Three combination vaccines that contain Hib conjugate vaccine are also available.

***Haemophilus influenzae* type b Conjugate Vaccines**

Vaccine	Protein Carrier	Manufacturer
PRP-T (ActHIB)	Tetanus toxoid	sanofi pasteur
PRP-OMP (PedvaxHIB)	Meningococcal group B outer membrane protein	Merck

Immunogenicity and Vaccine Efficacy

Both Hib conjugate vaccines licensed for use in infants are highly immunogenic. More than 95% of infants will develop protective antibody levels after a primary series of two or three doses. Clinical efficacy has been estimated at 95% to 100%. Invasive Hib disease in a completely vaccinated infant is uncommon.

Hib vaccine is immunogenic in patients with increased risk for invasive disease, such as those with sickle-cell disease, leukemia, or human immunodeficiency virus (HIV) infection, and those who have had a splenectomy. However, in persons with HIV infection, immunogenicity varies with stage of infection and degree of immunocompromise. Efficacy studies have not been performed in populations with increased risk of invasive disease.

Vaccination Schedule and Use

All infants, including those born prematurely, should receive a primary series of conjugate Hib vaccine (separate or in combination), beginning at 2 months of age. The number of doses in the primary series depends on the type of vaccine used. A primary series of PRP-OMP (PedvaxHIB) vaccine is two doses; PRP-T (ActHIB) requires a three-dose primary series (see table below). A booster is recommended at 12–15 months regardless of which vaccine is used for the primary series.

ACIP-Recommended *Haemophilus influenzae* type b (Hib) Routine Vaccination Schedule

Vaccine	2 Months	4 Months	6 Months	12-15 Months
PRP-T	Dose 1	Dose 2	Dose 3	Booster
PRP-OMP	Dose 1	Dose 2		Booster

***Haemophilus influenzae* type b Vaccine**

- Recommended interval 8 weeks for primary series doses
- Minimum interval 4 weeks for primary series doses
- Vaccination at younger than 6 weeks of age may induce immunologic tolerance to Hib antigen
- Minimum age 6 weeks

The recommended interval between primary series doses is 8 weeks, with a minimum interval of 4 weeks. At least 8 weeks should separate the booster dose from the previous (second or third) dose. Hib vaccines may be given simultaneously with all other vaccines.

Limited data suggest that Hib conjugate vaccines given before 6 weeks of age may induce immunologic tolerance to subsequent doses of Hib vaccine. A dose given before 6 weeks of age may reduce the response to subsequent doses. As a result, Hib vaccines, including combination vaccines that contain Hib conjugate, should never be given to a child younger than 6 weeks of age.

***Haemophilus influenzae* type b Vaccine Delayed Vaccination Schedule**

- Children starting late may not need entire 3 or 4 dose series
- Number of doses child requires depends on current age
- All children 15-59 months of age need at least 1 dose

The conjugate Hib vaccines licensed for use in infants are interchangeable. A series that includes vaccine of more than one type will induce a protective antibody level. If a child receives different brands of Hib vaccine at 2 and 4 months of age, a third dose of either brand should be administered at 6 months of age to complete the primary series. Either vaccine may be used for the booster dose, regardless of what was administered in the primary series.

Unvaccinated children 7 months of age and older may not require a full series of three or four doses. The number of

doses a child needs to complete the series depends on the child's current age.

Detailed Vaccination Schedule for *Haemophilus influenzae* type b Conjugate Vaccines

Vaccine	Age at 1st Dose (Months)	Primary Series	Booster
PRP-T (ActHIB)	2-6	3 doses, 2 months apart	12-15 months*
	7-11	2 doses, 2 months apart	12-15 months*
	12-14	1 dose	2 months later
	15-59	1 dose	—
PRP-OMP (PedvaxHIB)	2-6	2 doses, 2 months apart	12-15 months*
	7-11	2 doses, 2 months apart	12-15 months*
	12-14	1 dose	2 months later
	15-59	1 dose	—

*At least 2 months after previous dose

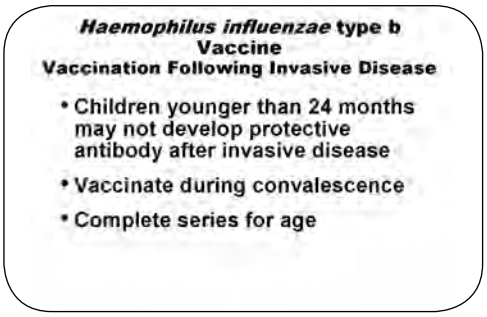
PRP-T (ActHIB)

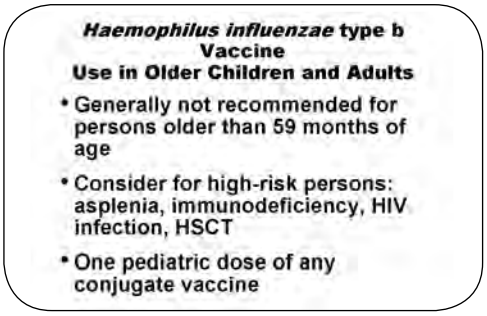
Previously unvaccinated infants aged 2 through 6 months should receive three doses of vaccine administered 2 months apart, followed by a booster dose at age 12–15 months, administered at least 2 months after the last dose. Unvaccinated children aged 7 through 11 months should receive two doses of vaccine 2 months apart, followed by a booster dose at age 12–15 months, administered at least 2 months after the last dose. Unvaccinated children aged 12 through 14 months should receive two doses of vaccine, at least 2 months apart. Any previously unvaccinated child aged 15 through 59 months should receive a single dose of vaccine.

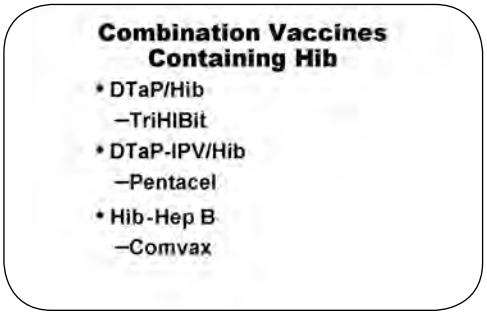
PRP-OMP (PedvaxHIB)

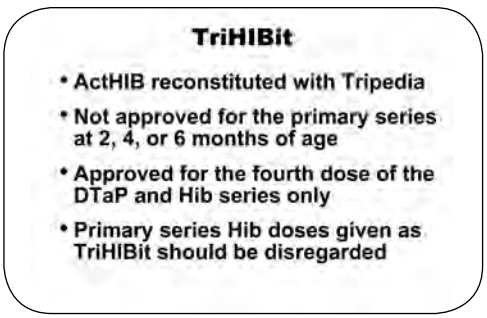
Unvaccinated children aged 2 through 11 months should receive two doses of vaccine 2 months apart, followed by a booster dose at 12–15 months of age, at least 2 months after the last dose. Unvaccinated children aged 12 through 14 months should receive two doses of vaccine 2 months apart. Any previously unvaccinated child 15 through 59 months of age should receive a single dose of vaccine.

Children with a lapsed Hib immunization series (i.e., children who have received one or more doses of Hib-containing vaccine but are not up-to-date for their age) may not need all the remaining doses of a three- or four-dose series. Vaccination of children with a lapsed schedule is addressed









in the catch-up schedule, published annually with the childhood vaccination schedule.

Hib invasive disease does not always result in development of protective anti-PRP antibody levels. Children younger than 24 months of age who develop invasive Hib disease should be considered susceptible and should receive Hib vaccine. Vaccination of these children should start as soon as possible during the convalescent phase of the illness. The schedule should be completed as recommended for the child's age.

Vaccination of Older Children and Adults

In general, Hib vaccination of persons older than 59 months of age is not recommended. The majority of older children are immune to Hib, probably from asymptomatic infection as infants. However, some older children and adults are at increased risk for invasive Hib disease and may be vaccinated if they were not vaccinated in childhood. These include those with functional or anatomic asplenia (e.g., sickle cell disease, postsplenectomy), immunodeficiency (in particular, persons with IgG2 subclass deficiency), immunosuppression from cancer chemotherapy, infection with HIV, and receipt of a hematopoietic stem cell transplant (HSCT). Previously unvaccinated persons older than 59 months of age with one of these high-risk conditions should be given at least one pediatric dose of any Hib conjugate vaccine.

Combination Vaccines

Three combination vaccines that contain *H. influenzae* type b are available in the United States—DTaP/Hib (TriHIBit, sanofi pasteur), DTaP-IPV-Hib (Pentacel, sanofi pasteur) and hepatitis B–Hib (Comvax, Merck).

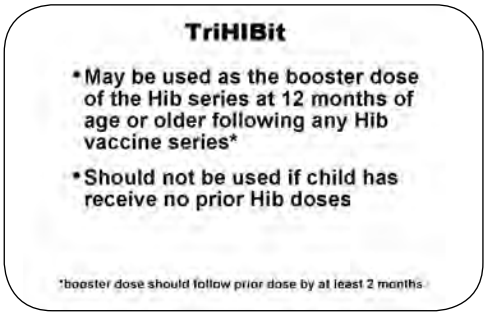
TriHIBit

TriHIBit was licensed for use in the United States in September 1996. The vaccines are packaged together in separate vials, and the DTaP component (Tripedia) is used to reconstitute the Hib component (ActHIB). No other brand of DTaP and Hib vaccine may be used to produce this combination (e.g., Infanrix must not be substituted for Tripedia). In addition, when supplied as TriHIBit, the DTaP and Hib components have a single lot number. Providers should generally use only the DTaP and Hib supplied together as TriHIBit. However, it is acceptable to combine Tripedia and ActHIB that have been supplied separately (i.e., not packaged as TriHIBit). In this situation, the lot numbers of both vaccines should be recorded.

TriHIBit is not approved by the Food and Drug Administration for use as the primary series at 2, 4, or 6 months of age. It is approved only for the fourth dose of the

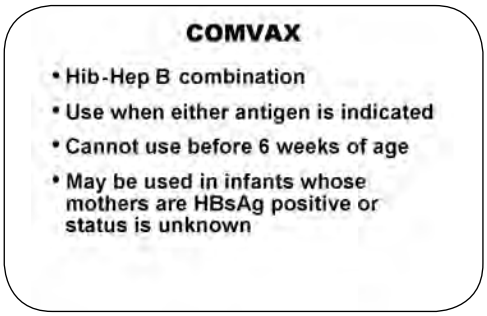
DTaP and Hib series. If TriHIBit is administered as one or more doses of the primary series at 2, 4, or 6 months of age, the Hib doses should be disregarded, and the child should be revaccinated as age-appropriate for Hib. The DTaP doses may be counted as valid and do not need to be repeated.

Although TriHIBit cannot be used in the primary series at 2, 4, or 6 months of age, it may be used as the booster (final) dose following a series of single-antigen Hib vaccine or combination hepatitis B–Hib vaccine (Comvax). Therefore, TriHIBit can be used if the child is 12 months of age or older and has received at least one prior dose of Hib vaccine 2 or more months earlier and TriHIBit will be the last dose in the Hib series. For example, TriHIBit can be used for the booster dose at 12 through 15 months of age in a child who has received Comvax or PedvaxHib at 2 and 4 months of age, or three prior doses of HibTiter or ActHib. TriHIBit can also be used at 15 through 59 months of age in a child who has received at least one prior dose of any Hib-containing vaccine. TriHIBit should not be used if the child has received no prior Hib doses.

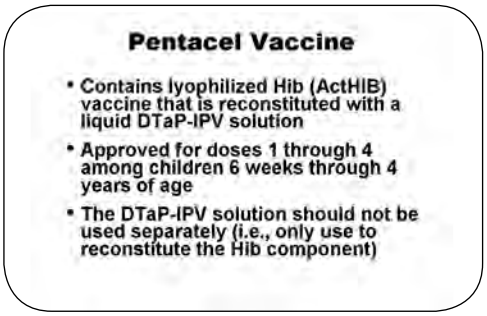


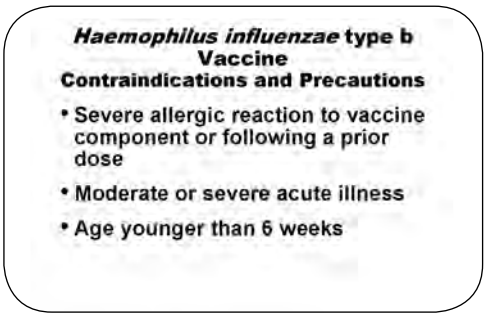
Comvax

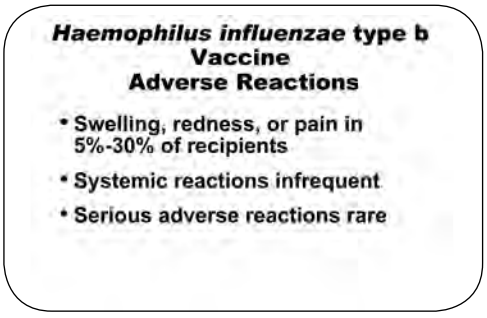
Comvax is a combination hepatitis B–Hib vaccine, licensed in October 1996. The vaccine contains a standard dose of PRP-OMP (PedvaxHIB), and 5 mcg (pediatric dose) of Merck's hepatitis B vaccine. Comvax is licensed for use when either or both antigens are indicated. However, because of the potential of immune tolerance to the Hib antigen, Comvax should not be used in infants younger than 6 weeks of age (i.e., the birth dose of hepatitis B, or a dose at 1 month of age, if the infant is on a 0-1-6-month schedule). Comvax is not licensed for infants whose mothers are known to be hepatitis B surface antigen positive (i.e., acute or chronic infection with hepatitis B virus). However, the vaccine contains the same dose of Merck's hepatitis B vaccine recommended for these infants, so response to the hepatitis B component of Comvax should be adequate. The Advisory Committee on Immunization Practices (ACIP) has approved off-label use of Comvax in children whose mother is HBsAg positive or whose HBsAg status is unknown. See http://www.cdc.gov/vaccines/programs/vfc/downloads/resolutions/1003hepb.pdf.



Recommendations for spacing and timing of Comvax are the same as those for the individual antigens. In particular, the third dose must be given at 12 months of age or older and at least 2 months after the second dose, as recommended for PRP-OMP.







Pentacel

Pentacel is a combination vaccine that contains lyophilized Hib (ActHIB) vaccine that is reconstituted with a liquid DTaP-IPV solution. The vaccine was licensed by FDA in June 2008. Pentacel is licensed by FDA for doses 1 through 4 of the DTaP series among children 6 weeks through 4 years of age. Pentacel should not be used for the fifth dose of the DTaP series, or for children 5 years or older regardless of the number of prior doses of the component vaccines. The DTaP-IPV solution is licensed only for use as the diluent for the lyophilized Hib component and should not be used separately.

Contraindications and Precautions to Vaccination

Vaccination with Hib conjugate vaccine is contraindicated for persons known to have experienced a severe allergic reaction (anaphylaxis) to a vaccine component or following a prior dose of that vaccine. Vaccination should be delayed for children with moderate or severe acute illnesses. Minor illnesses (e.g., mild upper respiratory infection) are not contraindications to vaccination. Hib conjugate vaccines are contraindicated for children younger than 6 weeks of age because of the potential for development of immunologic tolerance.

Contraindications and precautions for the use of TriHIBit, Pentacel, and Comvax are the same as those for its individual component vaccines (i.e., DTaP, Hib, IPV, and hepatitis B).

Adverse Reactions Following Vaccination

Adverse reaction following Hib conjugate vaccines are not common. Swelling, redness, or pain have been reported in 5%–30% of recipients and usually resolve within 12–24 hours. Systemic reactions such as fever and irritability are infrequent. Serious adverse reactions are rare. Available information on adverse reactions suggests that the risks for local and systemic reactions following TriHIBit administration are similar to those following concurrent administration of its individual component vaccines, and are probably due to the DTaP vaccine.

All serious adverse events that occur after receipt of any vaccine should be reported to the Vaccine Adverse Event Reporting System (VAERS) (http://vaers.hhs.gov/).

Vaccine Storage and Handling

All Hib conjugate vaccines should be shipped in insulated containers to prevent freezing. Unreconstituted or liquid vaccine should be stored at refrigerator temperature (35°–46°F [2°–8°C]). Hib vaccine must not be frozen.

ActHIB should be used within 24 hours of reconstitution and TriHIBit should be used immediately (within 30 minutes).

Surveillance and Reporting of Hib Disease

Invasive Hib disease is a reportable condition in most states. All healthcare personnel should report any case of invasive Hib disease to local and state health departments.

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Haemophilus influenzae type b

6

Hepatitis A

The first descriptions of hepatitis (epidemic jaundice) are generally attributed to Hippocrates. Outbreaks of jaundice, probably hepatitis A, were reported in the 17th and 18th centuries, particularly in association with military campaigns. Hepatitis A (formerly called infectious hepatitis) was first differentiated epidemiologically from hepatitis B, which has a long incubation period, in the 1940s. Development of serologic tests allowed definitive diagnosis of hepatitis B. In the 1970s, identification of the virus, and development of serologic tests helped differentiate hepatitis A from other types of non-B hepatitis.

Until 2004, hepatitis A was the most frequently reported type of hepatitis in the United States. In the prevaccine era, the primary methods used for preventing hepatitis A were hygienic measures and passive protection with immune globulin (IG). Hepatitis A vaccines were licensed in 1995 and 1996. These vaccines provide long-term protection against hepatitis A virus (HAV) infection. The similarities between the epidemiology of hepatitis A and poliomyelitis suggest that widespread vaccination of appropriate susceptible populations can substantially lower disease incidence, eliminate virus transmission, and ultimately, eliminate HAV infection.

Hepatitis A

- Epidemic jaundice described by Hippocrates
- Differentiated from hepatitis B in 1940s
- Serologic tests developed in 1970s
- Vaccines licensed in 1995 and 1996

Hepatitis A Virus

Hepatitis A is caused by infection with HAV, a nonenveloped RNA virus that is classified as a picornavirus. It was first isolated in 1979. Humans are the only natural host, although several nonhuman primates have been infected in laboratory conditions. Depending on conditions, HAV can be stable in the environment for months. The virus is relatively stable at low pH levels and moderate temperatures but can be inactivated by high temperature (185°F [85°C] or higher), formalin, and chlorine.

Hepatitis A Virus

- Picornavirus (RNA)
- Humans are only natural host
- Stable at low pH
- Inactivated by high temperature (185°F or higher), formalin, chlorine

Pathogenesis

HAV is acquired by mouth (through fecal-oral transmission) and replicates in the liver. After 10–12 days, virus is present in blood and is excreted via the biliary system into the feces. Peak titers occur during the 2 weeks before onset of illness. Although virus is present in serum, its concentration is several orders of magnitude less than in feces. Virus excretion begins to decline at the onset of clinical illness, and has decreased significantly by 7–10 days after onset of symptoms. Most infected persons no longer excrete virus in the feces by the third week of illness. Children may excrete virus longer than adults.

Hepatitis A Pathogenesis

- Entry into mouth
- Viral replication in the liver
- Virus present in blood and feces 10-12 days after infection
- Virus excretion may continue for up to 3 weeks after onset of symptoms

Hepatitis A

Hepatitis A Clinical Features

- Incubation period 28 days (range 15-50 days)
- Illness not specific for hepatitis A
- Likelihood of symptomatic illness directly related to age
- Children generally asymptomatic, adults symptomatic

Clinical Features

The incubation period of hepatitis A is approximately 28 days (range 15–50 days). The clinical course of acute hepatitis A is indistinguishable from that of other types of acute viral hepatitis. The illness typically has an abrupt onset of fever, malaise, anorexia, nausea, abdominal discomfort, dark urine and jaundice. Clinical illness usually does not last longer than 2 months, although 10%–15% of persons have prolonged or relapsing signs and symptoms for up to 6 months. Virus may be excreted during a relapse.

The likelihood of symptomatic illness from HAV infection is directly related to age. In children younger than 6 years of age, most (70%) infections are asymptomatic. In older children and adults, infection is usually symptomatic, with jaundice occurring in more than 70% of patients. HAV infection occasionally produces fulminant hepatitis A.

Complications

In the prevaccine era, fulminant hepatitis A caused about 100 deaths per year in the United States. The case-fatality rate among persons of all ages with reported cases was approximately 0.3% but could be higher among older persons (approximately 2% among persons 40 years of age and older).

Hepatitis A results in substantial morbidity, with associated costs caused by medical care and work loss. Hospitalization rates for hepatitis A are 11%–22%. Adults who become ill lose an average of 27 work days per illness, and health departments incur the costs of postexposure prophylaxis for an average of 11 contacts per case. Average direct and indirect costs of hepatitis A range from $1,817 to $2,459 per adult case and $433 to $1,492 per pediatric case. In 1989, the estimated annual U.S. total cost of hepatitis A was more than $200 million.

Laboratory Diagnosis

Hepatitis A cannot be distinguished from other types of viral hepatitis on the basis of clinical or epidemiologic features alone. Serologic testing is required to confirm the diagnosis. Virtually all patients with acute hepatitis A have detectable IgM anti-HAV. Acute HAV infection is confirmed during the acute or early convalescent phase of infection by the presence of IgM anti-HAV in serum. IgM generally becomes detectable 5–10 days before the onset of symptoms and can persist for up to 6 months.

IgG anti-HAV appears in the convalescent phase of infection, remains present in serum for the lifetime of the person, and confers enduring protection against disease.

The antibody test for total anti-HAV measures both IgG anti-HAV and IgM anti-HAV. Persons who are total anti-HAV positive and IgM anti-HAV negative have serologic markers indicating immunity consistent with either past infection or vaccination.

Molecular virology methods such as polymerase chain reaction (PCR)-based assays can be used to amplify and sequence viral genomes. These assays are helpful to investigate common-source outbreaks of hepatitis A. Providers with questions about molecular virology methods should consult with their state health department or the CDC Division of Viral Hepatitis.

Medical Management

There is no specific treatment for hepatitis A virus infection. Treatment and management of HAV infection are supportive.

Epidemiology

Occurrence

Hepatitis A occurs throughout the world. It is highly endemic in some areas, particularly Central and South America, Africa, the Middle East, Asia, and the Western Pacific.

Hepatitis A Epidemiology

• Reservoir	Human
• Transmission	Fecal-oral
• Temporal pattern	None
• Communicability	2 weeks before to 1 week after onset

Reservoir

Humans are the only natural reservoir of the virus. There are no insect or animal vectors. A chronic HAV carrier state has not been reported.

Transmission

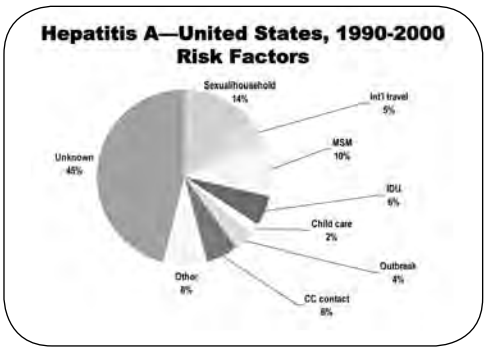
HAV infection is acquired primarily by the fecal-oral route by either person-to-person contact or ingestion of contaminated food or water. Because the virus is present in blood during the illness prodrome, HAV has been transmitted on rare occasions by transfusion. Although HAV may be present in saliva, transmission by saliva has not been demonstrated. Waterborne outbreaks are infrequent and are usually associated with sewage-contaminated or inadequately treated water.

Temporal Pattern

There is no appreciable seasonal variation in hepatitis A incidence.

Communicability

Viral shedding persists for 1 to 3 weeks. Infected persons are most likely to transmit HAV 1 to 2 weeks before the onset of



illness, when HAV concentration in stool is highest. The risk then decreases and is minimal the week after the onset of jaundice.

Risk Factors

From 1990 through 2000, the most frequently reported source of infection was personal contact (sexual or household) with an infected person (14%). Two percent of cases involved a child or employee in child care; 6% occurred in a contact of a child or employee in child care; 5% occurred among persons reporting recent international travel; and 4% occurred in the context of a recognized foodborne outbreak. Injection-drug use was a reported risk factor in 6% of cases; men who have sex with men represented 10% of cases. Forty-five percent of reported hepatitis A case-patients could not identify a risk factor for their infection.

Groups at increased risk for hepatitis A or its complications include international travelers, men who have sex with men, and users of illegal drugs. Outbreaks of hepatitis A have also been reported among persons working with hepatitis A–infected primates. This is the only occupational group known to be at increased risk for hepatitis A.

Persons with chronic liver disease are not at increased risk of infection but are at increased risk of acquiring fulminant hepatitis A. Persons with clotting factor disorders may be at increased risk of HAV because of administration of solvent/detergent-treated factor VIII and IX concentrates.

Foodhandlers are not at increased risk for hepatitis A because of their occupation, but are noteworthy because of their critical role in common-source foodborne HAV transmission. Healthcare personnel do not have an increased prevalence of HAV infections, and nosocomial HAV transmission is rare. Nonetheless, outbreaks have been observed in neonatal intensive care units and in association with adult fecal incontinence. Institutions for persons with developmental disabilities previously were sites of high HAV endemicity. But as fewer children have been institutionalized and conditions within these institutions have improved, HAV incidence and prevalence have decreased. However, sporadic outbreaks can occur. Schools are not common sites for HAV transmission. Multiple cases among children at a school require investigation of a common source. Workers exposed to sewage have not reported any work-related HAV infection in the United States, but serologic data are not available.

Children play an important role in HAV transmission. Children generally have asymptomatic or unrecognized illnesses, so they may serve as a source of infection, particularly for household or other close contacts.

Secular Trends in the United States

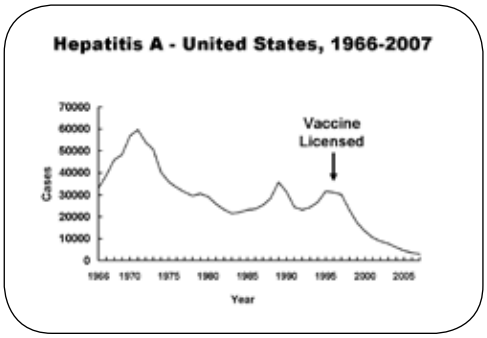
In the United States, hepatitis A has occurred in large nationwide epidemics approximately every 10 years, with the last increase in cases in 1989. However, between epidemics HAV infection continues to occur at relatively high rates. Hepatitis A became nationally reportable as a distinct entity in 1966. The largest number of cases reported in one year (59,606) was in 1971. A total of 5,970 cases was reported in 2004. After adjusting for under-reporting, 20,000 infections are estimated to have occurred in 2004, approximately half of which were symptomatic. Hepatitis A rates have been declining since 1995, and since 1998 have been at historically low levels. A total of 2,979 cases was reported in 2007. The wider use of vaccine is probably contributing to this marked decrease in hepatitis A rates in the United States.

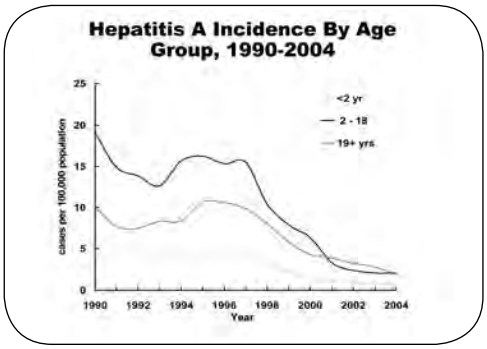
Historically, children 2 through 18 years of age have had the highest rates of hepatitis A (15 to 20 cases per 100,000 population in the early to mid-1990s). Since 2002, rates among children have declined and the incidence of hepatitis A is now similar in all age groups.

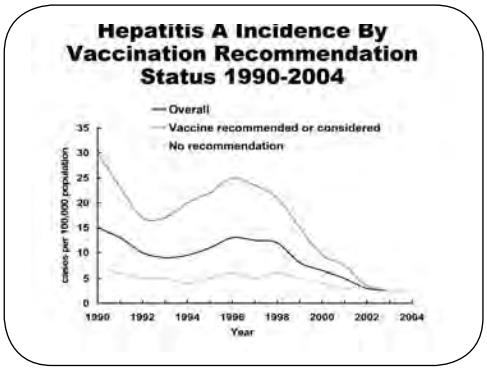
Based on testing from phase 1 of the Third National Health and Nutrition Examination Survey (NHANES III) conducted during 1988 through 1994, the prevalence of total antibody to HAV (anti-HAV) among the general U.S. population is 33%. Seroprevalence of HAV antibody increases with age, from 9% among 6- to 11-year-olds to 75% among persons 70 years of age and older. Anti-HAV prevalence is highest among Mexican-Americans (70%), compared with blacks (39%) and whites (23%). Anti-HAV prevalence is inversely related to income.

Prior to 2000, the incidence of reported hepatitis A was substantially higher in the western United States than in other parts of the country. From 1987 to 1997, 11 mostly western states (Arizona, Alaska, Oregon, New Mexico, Utah, Washington, Oklahoma, South Dakota, Idaho, Nevada, California) accounted for 50% of all reported cases but only 22% of the U.S. population. Many of these high-incidence states began routine hepatitis A vaccination programs for children in the late 1990s. Since 2002, rates have been similar in all parts of the country.

Many hepatitis A cases in the United States occur in the context of communitywide epidemics. Communities that experience such epidemics can be classified as high-rate and intermediate-rate communities. High-rate communities typically have epidemics every 5 to 10 years that may last for several years with substantial rates of disease (as high as 700 cases per 100,000 population annually







during outbreaks) but few cases among persons 15 years of age and older. These communities often are relatively well-defined either geographically or ethnically and include Native American, Alaska Native, Pacific Islander, and selected Hispanic communities and certain religious communities. Experience with hepatitis A vaccination programs in these high-rate communities has shown that when relatively high (65% to 80%) first-dose vaccination coverage of preschool and school-age children is achieved and routine vaccination of young children is sustained, ongoing outbreaks of hepatitis A could be interrupted. In these areas, sustained reduction in HAV incidence has been achieved and subsequent outbreaks have been prevented.

Case Definition

The case definition for hepatitis A was approved by the Council of State and Territorial Epidemiologists (CSTE) in 1997. It reflects a clinical diagnosis of hepatitis and, because HAV cannot be differentiated from other types of viral hepatitis on clinical or epidemiologic features alone, serologic evidence of HAV-specific IgM antibody is necessary.

The clinical case definition for hepatitis A is an acute illness with discrete onset of symptoms, and jaundice or elevated serum aminotransferase levels. The laboratory criterion for diagnosis is a positive IgM anti-HAV.

Hepatitis A Vaccine

Characteristics

Hepatitis A Vaccines

- Inactivated whole virus vaccines
- Pediatric and adult formulations
  - —pediatric formulations approved for persons 12 months through 18 years
  - —adult formulations approved for persons 19 years and older

Two inactivated whole-virus hepatitis A vaccines are available: HAVRIX (GlaxoSmithKline) and VAQTA (Merck). To produce each vaccine, cell culture–adapted virus is propagated in human fibroblasts, purified from cell lysates, inactivated with formalin, and adsorbed to an aluminum hydroxide adjuvant. HAVRIX is prepared with a preservative (2-phenoxyathanol); VAQTA does not contain a preservative. Both vaccines are available in both pediatric and adult formulations. The pediatric formulations of both vaccines are approved for persons 12 months through 18 years. The adult formulations are approved for persons 19 years and older.

Immunogenicity and Vaccine Efficacy

Hepatitis A Vaccine Immunogenicity

Adults
- >95% seropositive after one dose
- 100% seropositive after two doses

Children (≥12 months) and Adolescents
- >97% seropositive after one
- 100% seropositive after 2 doses

Both vaccines are highly immunogenic. More than 95% of adults will develop protective antibody within 4 weeks of a single dose of either vaccine, and nearly 100% will seroconvert after receiving two doses. Among children and adolescents, more than 97% will be seropositive within a

month of the first dose. In clinical trials, all recipients had protective levels of antibody after two doses.

Both vaccines are highly effective in preventing clinical hepatitis A. The efficacy of HAVRIX in protecting against clinical hepatitis A was 94% among 40,000 Thai children 1 to 16 years of age who received two doses 1 month apart while living in villages with high HAV disease rates. The efficacy of VAQTA in protecting against clinical hepatitis A was 100% among 1,000 New York children 2 to 16 years of age who received one dose while living in a community with a high HAV disease rate.

Data concerning the long-term persistence of antibody and immune memory are limited because the current vaccines have been available only since 1995 and 1996. Estimates of antibody persistence derived from kinetic models of antibody decline indicate that protective levels of anti-HAV could be present for 20 years or longer. Other mechanisms (e.g., cellular) may contribute to long-term protection, but this is unknown. The need for booster doses will be determined by postmarketing surveillance studies.

Vaccination Schedule and Use

Following its introduction in 1995, hepatitis A vaccine was primarily targeted to persons at increased risk for HAV infection, particularly international travelers. While this strategy prevented infection in this group and in other vaccinated individuals, it had little or no impact on the incidence of HAV infection in the United States.

As a result of successful vaccination programs in areas with a high incidence of HAV infection, the Advisory Committee on Immunization Practices (ACIP) in 1999 recommended that routine vaccination of children 2 years of age and older with hepatitis A vaccine be implemented in states, counties or communities where the average annual incidence of hepatitis A during 1987 through 1997 was 20 cases per 100,000 population or higher (i.e., at least twice the U.S. average of 10 cases per 100,000 population). ACIP also recommended that routine vaccination be considered for states, counties or communities where the average annual incidence of hepatitis A during 1987 through 1997 was 10 or more cases but less than 20 cases per 100,000 population. These strategies appear to have significantly reduced the incidence of hepatitis A in these areas.

Based on the successful implementation of childhood hepatitis A vaccination programs in high incidence areas, ACIP recommended in 2005 that all children should receive hepatitis A vaccine at 12 through 23 months of age. Vaccination should be integrated into the routine

Hepatitis A Vaccine Efficacy

HAVRIX
- 40,000 Thai children 1-16 years of age
- vaccine efficacy 94%

VAQTA
- 1,000 New York children 2-16 years of age
- vaccine efficacy 100%

ACIP Recommendation for Routine Hepatitis A Vaccination of Children

- All children should receive hepatitis A vaccine at 12-23 months of age
- Vaccination should be integrated into the routine childhood vaccination schedule
- Children who are not vaccinated by 2 years of age can be vaccinated at subsequent visits

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ACIP Recommendation for Routine Hepatitis A Vaccination of Children

- States, counties, and communities with existing hepatitis A vaccination programs for children 2 through 18 years of age should maintain these programs
- New efforts focused on routine vaccination of children 12 months of age should enhance, not replace ongoing vaccination programs for older children

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childhood vaccination schedule. Children who are not vaccinated by 2 years of age can be vaccinated at subsequent visits. ACIP encourages states, counties, and communities with existing hepatitis A vaccination programs for children 2 through 18 years of age to maintain these programs.

Persons at increased risk for HAV infection, or who are at increased risk for complications of HAV infection, should continue to be routinely vaccinated.

HAVRIX is available in two formulations: pediatric (720 ELISA units [EL.U.] per 0.5-mL dose) and adult (1,440 EL.U. per 1.0-mL dose). Children 1 through 18 years of age should receive a single primary dose of the pediatric formulation followed by a booster dose 6 to 12 months later. Adults 19 years of age and older receive one dose of the adult formulation followed by a booster 6 to 12 months later. The vaccine should be administered intramuscularly into the deltoid muscle. A needle length appropriate for the vaccinee's age and size (minimum of 1 inch) should be used.

Recommended Doses of Havrix® Hepatitis A Vaccine

Group	Age	Dose (EL.U.)	Volume	No. Doses	Schedule*
Children and Adolescents	1-18 years	720	0.5 mL	2	0, 6-12
Adults	≥ 19 years	1,440	1.0 mL	2	0, 6-12

*Months: 0 months represents timing of the initial dose; subsequent number(s) represent months after the initial dose.

VAQTA is quantified in units (U) of antigen and is available in pediatric and adult formulations. Children 1 through 18 years of age should receive one dose of pediatric formulation (25 U per dose) with a booster dose 6 to 18 months later. Adults 19 years of age and older should receive one dose of adult formulation (50 U per dose) with a booster dose 6 to 18 months after the first dose. The vaccine should be administered intramuscularly into the deltoid muscle. A needle length appropriate for the vaccinee's age and size should be used (minimum of 1 inch).

Recommended Doses of VAQTA® Hepatitis A Vaccine

Group	Age	Dose (U)	Volume	No. Doses	Schedule*
Children and Adolescents	1-18 years	25	0.5 mL	2	0, 6-18
Adults	≥ 19 years	50	1.0 mL	2	0, 6-18

*Months: 0 months represents timing of the initial dose; subsequent number(s) represent months after the initial dose.

Limited data indicate that vaccines from different manufacturers are interchangeable. Completion of the series with

the same product is preferable. However, if the originally used product is not available or not known, vaccination with either product is acceptable.

For both vaccines, the booster dose given should be based on the person's age at the time of the booster dose, not the age when the first dose was given. For example, if a person received the first dose of the pediatric formulation of VAQTA at 18 years of age, and returns for the booster dose at age 19 years, the booster dose should be the adult formulation, not the pediatric formulation.

The minimum interval between the first and booster doses of hepatitis A vaccine is 6 calendar months. If the interval between the first and booster doses of hepatitis A vaccine extends beyond 18 months, it is not necessary to repeat the first dose.

Hepatitis A Vaccines

Formulation	HAVRIX	VAQTA
Pediatric		
age	1-18 yrs	1-18 yrs
dose	0.5 ml	0.5 ml
Adult		
age	≥19 yrs	≥19 yrs
dose	1.0 ml	1.0 ml

Combination Hepatitis A and Hepatitis B Vaccine

In 2001, the Food and Drug Administration approved a combination hepatitis A and hepatitis B vaccine (Twinrix, GlaxoSmithKline). Each dose of Twinrix contains 720 EL.U. of hepatitis A vaccine (equivalent to a pediatric dose of HAVRIX), and 20 mcg of hepatitis B surface antigen protein (equivalent to an adult dose of Engerix-B). The vaccine is administered in a three-dose series at 0, 1, and 6 months. Appropriate spacing of the doses must be maintained to assure long-term protection from both vaccines. The first and second doses should be separated by at least 4 weeks, and the second and third doses should be separated by at least 5 months. Twinrix is approved for persons aged 18 years and older and can be used in persons in this age group with indications for both hepatitis A and hepatitis B vaccines.

Twinrix

- Combination hepatitis A vaccine (pediatric dose) and hepatitis B (adult dose)
- Schedule: 0, 1, 6 months
- Approved for persons 18 years of age and older

In 2007 FDA approved an alternative schedule for Twinrix with doses at 0,7, and 21 through 30 days and a booster dose 12 months after the first dose.

Because the hepatitis B component of Twinrix is equivalent to a standard dose of hepatitis B vaccine, the schedule is the same whether Twinrix or single-antigen hepatitis B vaccine is used.

Single-antigen hepatitis A vaccine may be used to complete a series begun with Twinrix and vice versa. A person 19 years of age or older who receives one dose of Twinrix may complete the hepatitis A series with two doses of adult formulation hepatitis A vaccine separated by at least 5 months. A person who receives two doses of Twinrix may complete the hepatitis A series with one dose of adult formulation hepatitis A vaccine or Twinrix 5 months after the second dose. A person who begins the hepatitis A series

with single-antigen hepatitis A vaccine may complete the series with two doses of Twinrix or one dose of adult formulation hepatitis A vaccine. An 18-year-old should follow the same schedule using the pediatric formulation.

Persons at Increased Risk for Hepatitis A or Severe Outcomes of Infection

Persons at increased risk for hepatitis A should be identified and vaccinated. Hepatitis A vaccine should be strongly considered for persons 1 year of age and older who are traveling to or working in countries where they would have a high or intermediate risk of hepatitis A virus infection. These areas include all areas of the world except Canada, Western Europe and Scandinavia, Japan, New Zealand, and Australia.

The first dose of hepatitis A vaccine should be administered as soon as travel is considered. For healthy persons 40 years of age or younger, 1 dose of single antigen vaccine administered at any time before departure can provide adequate protection.

Unvaccinated adults older than 40 years of age, immunocompromised persons, and persons with chronic liver disease planning to travel in 2 weeks or sooner should receive the first dose of vaccine and also can receive immune globulin at the same visit. Vaccine and IG should be administered with separate syringes at different anatomic sites.

Hepatitis A Vaccine Recommendations

- International travelers
- Men who have sex with men
- Persons who use illegal drugs
- Persons who have clotting factor disorders
- Persons with occupational risk
- Persons with chronic liver disease

Travelers who choose not to receive vaccine should receive a single dose of IG (0.02 mL/kg), which provides protection against HAV infection for up to 3 months. Persons whose travel period is more than 2 months should be administered IG at 0.06 mL/kg. IG should be repeated in 5 months for prolonged travel.

Other groups that should be offered vaccine include men who have sex with other men, persons who use illegal drugs, persons who have clotting factor disorders, and persons with occupational risk of infection. Persons with occupational risk include only those who work with hepatitis A-infected primates or with hepatitis A virus in a laboratory setting. No other groups have been shown to be at increased risk of hepatitis A infection due to occupational exposure.

Persons with chronic liver disease are not at increased risk for HAV infection because of their liver disease alone. However, these persons are at increased risk for fulminant hepatitis A should they become infected. Susceptible persons who have chronic liver disease should be vaccinated. Susceptible persons who either are awaiting or have received liver transplants should be vaccinated.

Hepatitis A vaccination is not routinely recommended for healthcare personnel, persons attending or working in child care centers, or persons who work in liquid or solid waste management (e.g., sewer workers or plumbers). These groups have not been shown to be at increased risk for hepatitis A infection. ACIP does not recommend routine hepatitis A vaccination for food service workers, but vaccination may be considered based on local epidemiology.

Hepatitis A Vaccine Recommendations

- Healthcare personnel not routinely recommended
- Child care centers: not routinely recommended
- Sewer workers or plumbers: not routinely recommended
- Food handlers: may be considered based on local circumstances

Prevaccination Serologic Testing

HAV infection produces lifelong immunity to hepatitis A, so there is no benefit of vaccinating someone with serologic evidence of past HAV infection. The risk for adverse events following vaccination of such persons is not higher than the risk for serologically negative persons. As a result, the decision to conduct prevaccination testing should be based chiefly on the prevalence of immunity, the cost of testing and vaccinating (including office visit costs), and the likelihood that testing will interfere with initiating vaccination.

Hepatitis A Serologic Testing

Prevaccination
- not indicated for children
- may be considered for some adults and older adolescents

Postvaccination
- not indicated

Testing of children is not indicated because of their expected low prevalence of infection. Persons for whom prevaccination serologic testing will likely be most cost-effective include adults who were either born in or lived for extensive periods in geographic areas that have a high endemicity of HAV infection (e.g., Central and South America, Africa, Asia); older adolescents and adults in certain populations (i.e., Native Americans, Alaska Natives, and Hispanics); adults in certain groups that have a high prevalence of infection (see above); and adults 40 years of age and older.

Commercially available tests for total anti-HAV should be used for prevaccination testing.

Postvaccination Serologic Testing

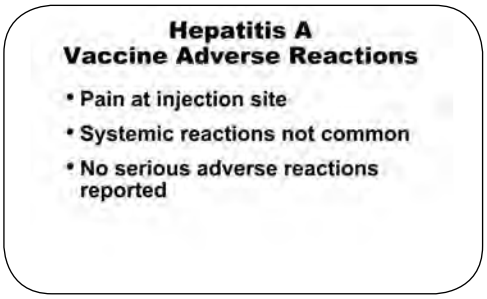
Postvaccination testing is not indicated because of the high rate of vaccine response among adults and children. Testing methods sufficiently sensitive to detect low anti-HAV concentrations after vaccination are not approved for routine diagnostic use in the United States.

Contraindications and Precautions to Vaccination

Hepatitis A vaccine should not be administered to persons with a history of a severe allergic reaction (anaphylaxis) to a vaccine component or following a prior dose of hepatitis A vaccine, hypersensitivity to alum or, in the case of HAVRIX, to the preservative 2-phenoxyethanol. Vaccination of persons with moderate or severe acute illnesses should be deferred until the person's condition has improved.

Hepatitis A Vaccine Contraindications and Precautions

- Severe allergic reaction to a vaccine component or following a prior dose
- Moderate or severe acute illness



The safety of hepatitis A vaccination during pregnancy has not been determined. However, because it is an inactivated vaccine, the theoretical risk to the fetus is low. The risk associated with vaccination should be weighed against the risk for HAV infection. Because hepatitis A vaccine is inactivated, no special precautions are needed when vaccinating immunocompromised persons, although response to the vaccine may be suboptimal.

Adverse Reactions Following Vaccination

For both vaccines, the most commonly reported adverse reaction following vaccination is a local reaction at the site of injection. Injection site pain, erythema, or swelling is reported by 20% to 50% of recipients. These symptoms are generally mild and self-limited. Mild systemic complaints (e.g., malaise, fatigue, low-grade fever) are reported by fewer than 10% of recipients. No serious adverse reactions have been reported.

Vaccine Storage and Handling

Hepatitis A vaccine should be stored and shipped at temperatures of 35°–46°F (2°–8°C) and should not be frozen. However, the reactogenicity and immunogenicity are not altered by storage for 1 week at 98.6°F (37°C).

Postexposure Prophylaxis

Immune globulin (IG) is typically used for postexposure prophylaxis of hepatitis A in susceptible persons. Hepatitis A vaccine may be used for postexposure prophylaxis in healthy persons 12 months through 40 years of age. Immune globulin is preferred for persons older than 40 years of age, children younger than 12 months of age, immunocompromised persons, and persons with chronic liver disease. See *MMWR* 2007;54(No.41):1080-84 (October 19, 2007) for details.

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Hepatitis A

7

Hepatitis B

Viral hepatitis is a term commonly used for several clinically similar yet etiologically and epidemiologically distinct diseases. Hepatitis A (formerly called infectious hepatitis) and hepatitis B (formerly called serum hepatitis) have been recognized as separate entities since the early 1940s and can be diagnosed with specific serologic tests. Delta hepatitis is an infection dependent on the hepatitis B virus (HBV). It may occur as a coinfection with acute HBV infection or as superinfection of an HBV carrier.

Hepatitis B

- Epidemic jaundice described by Hippocrates in 5th century BCE
- Jaundice reported among recipients of human serum and yellow fever vaccines in 1930s and 1940s
- Australia antigen described in 1965
- Serologic tests developed in 1970s

Epidemic jaundice was described by Hippocrates in the 5th century BCE. The first recorded cases of "serum hepatitis," or hepatitis B, are thought to be those that followed the administration of smallpox vaccine containing human lymph to shipyard workers in Germany in l883. In the early and middle parts of the 20th century, serum hepatitis was repeatedly observed following the use of contaminated needles and syringes. The role of blood as a vehicle for virus transmission was further emphasized in 1943, when Beeson described jaundice that had occurred in seven recipients of blood transfusions. Australia antigen, later called hepatitis B surface antigen (HBsAg), was first described in 1965, and the Dane particle (complete hepatitis B virion) was identified in 1970. Identification of serologic markers for HBV infection followed, which helped clarify the natural history of the disease. Ultimately, HBsAg was prepared in quantity and now comprises the immunogen in highly effective vaccines for prevention of HBV infection.

Hepatitis B Virus

HBV is a small, double-shelled virus in the family Hepadnaviridae. Other Hepadnaviridae include duck hepatitis virus, ground squirrel hepatitis virus, and woodchuck hepatitis virus. The virus has a small circular DNA genome that is partially double-stranded. HBV contains numerous antigenic components, including HBsAg, hepatitis B core antigen (HBcAg), and hepatitis B e antigen (HBeAg). Humans are the only known host for HBV, although some nonhuman primates have been infected in laboratory conditions. HBV is relatively resilient and, in some instances, has been shown to remain infectious on environmental surfaces for more than 7 days at room temperature.

Hepatitis B Virus

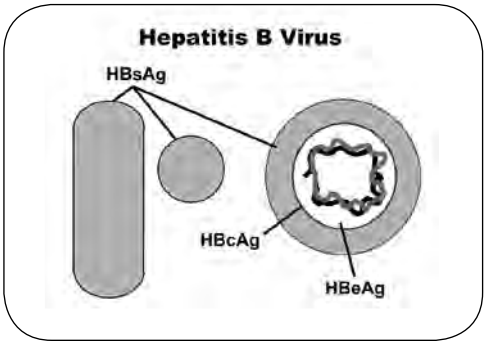
- Hepadnaviridae family (DNA)
- Numerous antigenic components
- Humans are only known host
- May retain infectivity for more than 7 days at room temperature

An estimated 2 billion persons worldwide have been infected with HBV, and more than 350 million persons have chronic, lifelong infections. HBV infection is an established cause of acute and chronic hepatitis and cirrhosis. It is the cause of up to 80% of hepatocellular carcinomas. The World Health Organization estimated that more than 600,000 persons died worldwide in 2002 of hepatitis B-associated acute and chronic liver disease.

Hepatitis B Virus Infection

- More than 350 million chronically infected worldwide
- Established cause of chronic hepatitis and cirrhosis
- Human carcinogen—cause of up to 80% of hepatocellular carcinomas

Hepatitis B



Several well-defined antigen–antibody systems are associated with HBV infection. HBsAg, formerly called Australia antigen or hepatitis-associated antigen, is an antigenic determinant found on the surface of the virus. It also makes up subviral 22-nm spherical and tubular particles. HBsAg can be identified in serum 30 to 60 days after exposure to HBV and persists for variable periods. HBsAg is not infectious. Only the complete virus (Dane particle) is infectious. However, when HBsAg is present in the blood, complete virus is also present, and the person may transmit the virus. During replication, HBV produces HBsAg in excess of that needed for production of Dane particles.

HBcAg is the nucleocapsid protein core of HBV. HBcAg is not detectable in serum by conventional techniques, but it can be detected in liver tissue of persons with acute or chronic HBV infection. HBeAg, a soluble protein, is also contained in the core of HBV. HBeAg is detected in the serum of persons with high virus titers and indicates high infectivity. Antibody to HBsAg (anti-HBs) develops during convalescence after acute HBV infection or following hepatitis B vaccination. The presence of anti-HBs indicates immunity to HBV. (Anti-HBs is sometimes referred to as HBsAb, but use of this term is discouraged because of potential confusion with HBsAg.) Antibody to HBcAg (anti-HBc) indicates infection with HBV at an undefined time in the past. IgM class antibody to HBcAg (IgM anti-HBc) indicates recent infection with HBV. Antibody to HBeAg (anti-HBe) becomes detectable when HBeAg is lost and is associated with low infectivity of serum.

Clinical Features

Hepatitis B Clinical Features

- Incubation period 60-150 days (average 90 days)
- Nonspecific prodrome of malaise, fever, headache, myalgia
- Illness not specific for hepatitis B
- At least 50% of infections asymptomatic

The clinical course of acute hepatitis B is indistinguishable from that of other types of acute viral hepatitis. The incubation period ranges from 60 to 150 days (average, 90 days). Clinical signs and symptoms occur more often in adults than in infants or children, who usually have an asymptomatic acute course. However, approximately 50% of adults who have acute infections are asymptomatic.

The preicteric, or prodromal phase from initial symptoms to onset of jaundice usually lasts from 3 to l0 days. It is nonspecific and is characterized by insidious onset of malaise, anorexia, nausea, vomiting, right upper quadrant abdominal pain, fever, headache, myalgia, skin rashes, arthralgia and arthritis, and dark urine, beginning 1 to 2 days before the onset of jaundice. The icteric phase is variable but usually lasts from l to 3 weeks and is characterized by jaundice, light or gray stools, hepatic tenderness and hepatomegaly (splenomegaly is less common). During convalescence, malaise and fatigue may persist for weeks or months, while jaundice, anorexia, and other symptoms disappear.

Most acute HBV infections in adults result in complete recovery with elimination of HBsAg from the blood and the production of anti-HBs, creating immunity to future infection.

Complications

While most acute HBV infections in adults result in complete recovery, fulminant hepatitis occurs in about 1% to 2% of acutely infected persons. About 200 to 300 Americans die of fulminant disease each year (case-fatality rate 63% to 93%). Although the consequences of acute HBV infection can be severe, most of the serious complications associated with HBV infection are due to chronic infection.

Hepatitis B Complications

- Fulminant hepatitis
- Hospitalization
- Cirrhosis
- Hepatocellular carcinoma
- Death

Chronic HBV Infection

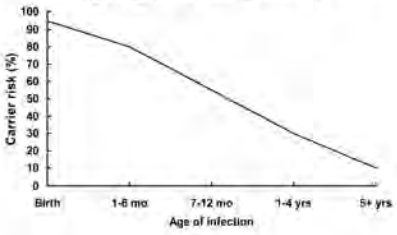
Approximately 5% of all acute HBV infections progress to chronic infection, with the risk of chronic HBV infection decreasing with age. As many as 90% of infants who acquire HBV infection from their mothers at birth become chronically infected. Of children who become infected with HBV between 1 year and 5 years of age, 30% to 50% become chronically infected. By adulthood, the risk of acquiring chronic HBV infection is approximately 5%.

Chronic Hepatitis B Virus Infection

- Chronic viremia
- Responsible for most mortality
- Overall risk 5%
- Higher risk with early infection

Persons with chronic infection are often asymptomatic and may not be aware that they are infected; however, they are capable of infecting others and have been referred to as carriers. Chronic infection is responsible for most HBV-related morbidity and mortality, including chronic hepatitis, cirrhosis, liver failure, and hepatocellular carcinoma. Approximately 25% of persons with chronic HBV infection die prematurely from cirrhosis or liver cancer. Chronic active hepatitis develops in more than 25% of carriers and often results in cirrhosis. An estimated 3,000 to 4,000 persons die of hepatitis B-related cirrhosis each year in the United States. Persons with chronic HBV infection are at 12 to 300 times higher risk of hepatocellular carcinoma than noncarriers. An estimated 1,000 to 1,500 persons die each year in the United States of hepatitis B-related liver cancer.

Risk of Chronic HBV Carriage by Age of Infection



Laboratory Diagnosis

Diagnosis is based on clinical, laboratory, and epidemiologic findings. HBV infection cannot be differentiated on the basis of clinical symptoms alone, and definitive diagnosis depends on the results of serologic testing. Serologic markers of HBV infection vary depending on whether the infection is acute or chronic.

HBsAg is the most commonly used test for diagnosing acute HBV infections or detecting carriers. HBsAg can be detected as early as 1 or 2 weeks and as late as 11 or 12

weeks after exposure to HBV when sensitive assays are used. The presence of HBsAg indicates that a person is infectious, regardless of whether the infection is acute or chronic.

Anti-HBc (core antibody) develops in all HBV infections, appears shortly after HBsAg in acute disease, and indicates HBV infection at some undefined time in the past. Anti-HBc only occurs after HBV infection and does not develop in persons whose immunity to HBV is from vaccine. Anti-HBc generally persists for life and is not a serologic marker for acute infection.

IgM anti-HBc appears in persons with acute disease about the time of illness onset and indicates recent infection with HBV. IgM anti-HBc is generally detectable 4 to 6 months after onset of illness and is the best serologic marker of acute HBV infection. A negative test for IgM-anti-HBc together with a positive test for HBsAg in a single blood sample identifies a chronic HBV infection.

Interpretation of Hepatitis B Serologic Tests

Tests	Results	Interpretation
HBsAg	Negative	Susceptible
anti-HBc	Negative	
anti-HBs	Negative	
HBsAg	Negative	Immune due to vaccination
anti-HBc	Negative	
anti-HBs	Positive with ≥10mIU/mL*	
HBsAg	Negative	Immune due to natural infection
anti-HBc	Positive	
anti-HBs	Positive	
HBsAg	Positive	Acutely infected
anti-HBc	Positive	
IgM anti-HBc	Positive	
anti-HBs	Negative	
HBsAg	Positive	Chronically infected
anti-HBc	Positive	
IgM anti-HBc	Negative	
anti-HBs	Negative	
HBsAg	Negative	Four interpretations possible†
anti-HBc	Positive	
anti-HBs	Negative	

*Postvaccination testing, when it is recommended, should be performed 1-2 months following dose #3.

† 1. May be recovering from acute HBV infection.
2. May be distantly immune and the test is not sensitive enough to detect a very low level of anti-HBs in serum.
3. May be susceptible with a false positive anti-HBc.
4. May be chronically infected and have an undetectable level of HBsAg present in the serum.

HBeAg is a useful marker associated strongly with the number of infective HBV particles in the serum and a higher risk of infectivity.

Anti-HBs (surface antibody) is a protective, neutralizing antibody. The presence of anti-HBs following acute HBV infection generally indicates recovery and immunity against reinfection. Anti-HBs can also be acquired as an immune response to hepatitis B vaccine or passively transferred by administration of hepatitis B immune globulin (HBIG). When using radioimmunoassay (RIA), a minimum of 10 sample ratio units should be used to designate immunity. With enzyme immunoassay (EIA), the manufacturer's recommended positive should be considered an appropriate measure of immunity. The level of anti-HBs may also be expressed in milli-international units/mL (mIU/mL). Ten mIU/mL is considered to indicate a protective level of immunity.

Medical Management

There is no specific therapy for acute HBV infection. Treatment is supportive. Interferon is the most effective treatment for chronic HBV infection and is successful in 25% to 50% of cases.

Persons with acute or chronic HBV infections should prevent their blood and other potentially infective body fluids from contacting other persons. They should not donate blood or share toothbrushes or razors with household members.

In the hospital setting, patients with HBV infection should be managed with standard precautions.

Epidemiology

Reservoir

Although other primates have been infected in laboratory conditions, HBV infection affects only humans. No animal or insect hosts or vectors are known to exist.

Transmission

The virus is transmitted by parenteral or mucosal exposure to HBsAg-positive body fluids from persons who have acute or chronic HBV infection. The highest concentrations of virus are in blood and serous fluids; lower titers are found in other fluids, such as saliva and semen. Saliva can be a vehicle of transmission through bites; however, other types of exposure to saliva, including kissing, are unlikely modes of transmission. There appears to be no transmission of HBV via tears, sweat, urine, stool, or droplet nuclei.

Hepatitis B Epidemiology

• Reservoir	Human
• Transmission	Bloodborne Subclinical cases transmit
• Communicability	1-2 months before and after onset of symptoms Chronic carriers

In the United States, the most important route of transmission is by sexual contact, either heterosexual or homosexual, with an infected person. Fecal-oral transmission does not appear to occur. However, transmission occurs among men who have sex with men, possibly via contamination from asymptomatic rectal mucosal lesions.

Direct percutaneous inoculation of HBV by needles during injection-drug use is an important mode of transmission. Transmission of HBV may also occur by other percutaneous exposure, including tattooing, ear piercing, and acupuncture, as well as needlesticks or other injuries from sharp instruments sustained by medical personnel. These exposures account for only a small proportion of reported cases in the United States. Breaks in the skin without overt needle puncture, such as fresh cutaneous scratches, abrasions, burns, or other lesions, may also serve as routes for entry.

Contamination of mucosal surfaces with infective serum or plasma may occur during mouth pipetting, eye splashes, or other direct contact with mucous membranes of the eyes or mouth, such as hand-to-mouth or hand-to-eye contact when hands are contaminated with infective blood or serum. Transfer of infective material to skin lesions or mucous membranes via inanimate environmental surfaces may occur by touching surfaces of various types of hospital equipment. Contamination of mucosal surfaces with infective secretions other than serum or plasma could occur with contact involving semen.

Hepatitis B Perinatal Transmission*

- If mother positive for HBsAg and HBeAg
  - –70%-90% of infants infected
  - –90% of infected infants become chronically infected
- If positive for HBsAg only
  - –10% of infants infected
  - –90% of infected infants become chronically infected

*in the absence of postexposure prophylaxis

Perinatal transmission from mother to infant at birth is very efficient. If the mother is positive for both HBsAg and HBeAg, 70%–90% of infants will become infected in the absence of postexposure prophylaxis. The risk of perinatal transmission is about 10% if the mother is positive only for HBsAg. As many as 90% of these infected infants will become chronically infected with HBV.

Global Patterns of Chronic HBV Infection

- High (≥8%): 45% of global population
  - –lifetime risk of infection >60%
  - –early childhood infections common
- Intermediate (2%-7%): 43% of global population
  - –lifetime risk of infection 20%-60%
  - –infections occur in all age groups
- Low (<2%): 12% of global population
  - –lifetime risk of infection <20%
  - –most infections occur in adult risk groups

The frequency of infection and patterns of transmission vary in different parts of the world. Approximately 45% of the global population live in areas with a high prevalence of chronic HBV infection (8% or more of the population is HBsAg positive), 43% in areas with a moderate prevalence (2% to 7% of the population is HBsAg positive), and 12% in areas with a low prevalence (less than 2% of the population is HBsAg positive).

In China, Southeast Asia, most of Africa, most Pacific Islands, parts of the Middle East, and the Amazon Basin, 8% to l5% of the population carry the virus. The lifetime risk of HBV infection is greater than 60%, and most infections are acquired at birth or during early childhood, when the risk of developing chronic infections is greatest. In these areas, because most infections are asymptomatic, very little acute

disease related to HBV occurs, but rates of chronic liver disease and liver cancer among adults are very high. In the United States, Western Europe, and Australia, HBV infection is a disease of low endemicity. Infection occurs primarily during adulthood, and only 0.1% to 0.5% of the population are chronic carriers. Lifetime risk of HBV infection is less than 20% in low prevalence areas.

Communicability

Persons with either acute or chronic HBV infection should be considered infectious any time that HBsAg is present in the blood. When symptoms are present in persons with acute HBV infection, HBsAg can be found in blood and body fluids for 1–2 months before and after the onset of symptoms.

Secular Trends in the United States

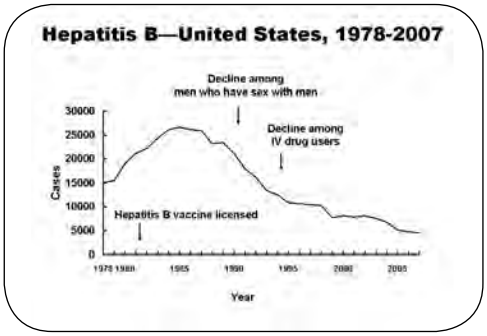
Hepatitis has been reportable in the United States for many years. Hepatitis B became reportable as a distinct entity during the 1970s, after serologic tests to differentiate different types of hepatitis became widely available.

The incidence of reported hepatitis B peaked in the mid-1980s, with about 26,000 cases reported each year. Reported cases have declined since that time, and fell below 10,000 cases for the first time in 1996. The decline in cases during the 1980s and early 1990s is generally attributed to reduction of transmission among men who have sex with men and injection-drug users as a result of HIV prevention efforts.

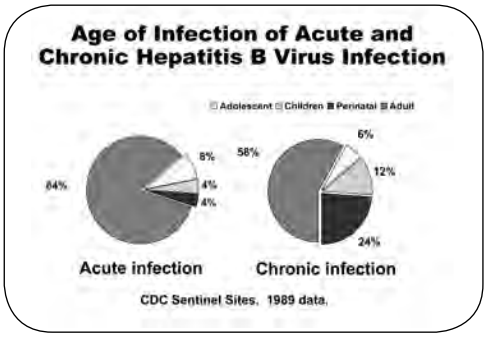
During 1990–2004, incidence of acute hepatitis B in the United States declined 75%. The greatest decline (94%) occurred among children and adolescents, coincident with an increase in hepatitis B vaccine coverage. A total of 4,519 cases of hepatitis B were reported in 2007.

Reported cases of HBV infection represent only a fraction of cases that actually occur. In 2001, a total of 7,844 cases of acute hepatitis B were reported to CDC. Based on these reports, CDC estimates that 22,000 acute cases of hepatitis B resulted from an estimated 78,000 new infections. An estimated 1–1.25 million persons in the United States are chronically infected with HBV, and an additional 5,000–8,000 persons become chronically infected each year.

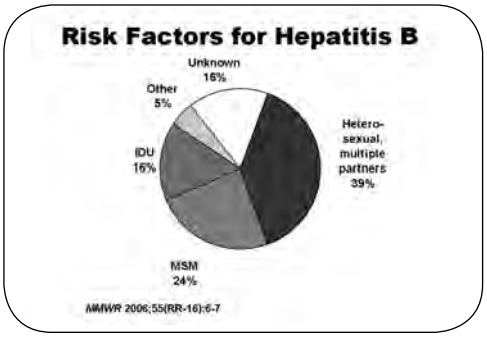
Before routine childhood hepatitis B vaccination was recommended, more than 80% of acute HBV infections occurred among adults. Adolescents accounted for approximately 8% of infections, and children and infants infected through perinatal transmission accounted for approximately 4% each. Perinatal transmission accounted for a disproportionate 24% of chronic infections.

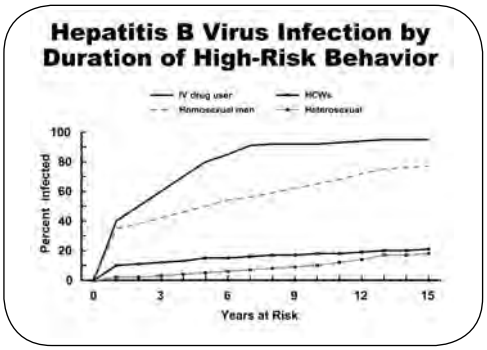






Hepatitis B





In the United States in 2005, the highest incidence of acute hepatitis B was among adults aged 25–45 years. Approximately 79% of persons with newly acquired hepatitis B infection are known to engage in high-risk sexual activity or injection-drug use. Other known exposures (i.e., occupational, household, travel, and healthcare-related) together account for 5% of new infections. Approximately 16% of persons deny a specific risk factor for infection.

Although HBV infection is uncommon among adults in the general population (the lifetime risk of infection is less than 20%), it is highly prevalent in certain groups. Risk for infection varies with occupation, lifestyle, or environment (see table). Generally, the highest risk for HBV infection is associated with lifestyles, occupations, or environments in which contact with blood from infected persons is frequent. In addition, the prevalence of HBV markers for acute or chronic infection increases with increasing number of years of high-risk behavior. For instance, an estimated 40% of injection-drug users become infected with HBV after 1 year of drug use, while more than 80% are infected after 10 years.

Prevalence of Hepatitis B in Various Population Groups

	Population Group	Prevalence of Serologic Markers of HBV Infection	
		HBsAg (%)	All Markers (%)
High-Risk	Immigrants/refugees from areas of high HBV endemicity.	13	70-85
	Clients in mental health institutions.	10-20	35-80
	Users of illicit parenteral drugs.	7	60-80
	Homosexually active men.	6	35-80
	Patients of hemodialysis units.	3-10	20-80
	Household contacts of HBV carriers.	3-6	30-60
Intermediate-Risk	Prisoners (male).	1-8	10-80
	Healthcare providers – frequent blood contact.	1-2	15-30
	Staff of mental health institutions.	1	10-25
	Heterosexuals with multiple partners.	0.5	5-20
Low-Risk	Healthcare providers – no or infrequent blood contact.	0.3	3-10
	Healthy adults (first-time volunteer blood donors).	0.3	3-5

Hepatitis B Prevention Strategies

Hepatitis B vaccines have been available in the United States since 1981. However, the impact of vaccine on HBV disease has been less than optimal.

The apparent lack of impact from the vaccine can be attributed to several factors. From 1981 until 1991, vaccination was targeted to persons in groups at high risk of acquiring HBV infection. A large proportion of persons with HBV infection (25% to 30%) deny having any risk factors for the disease. These persons would not be identified by a targeted risk factor screening approach.

The three major risk groups (heterosexuals with contact with infected persons or multiple partners, injection-drug users, and men who have sex with men) are not reached effectively by targeted programs. Deterrents to immunization of these groups include lack of awareness of the risk of disease and its consequences, lack of effective public or private sector programs, and vaccine cost. Difficulty in gaining access to these populations is also a problem. Further, success in providing vaccine to persons in high-risk groups has been limited because of rapid acquisition of infection after beginning high-risk behaviors, low initial vaccine acceptance, and low rates of completion of vaccinations.

A comprehensive strategy to eliminate hepatitis B virus transmission was recommended in 1991; it includes prenatal testing of pregnant women for HBsAg to identify newborns who require immunoprophylaxis for prevention of perinatal infection and to identify household contacts who should be vaccinated, routine vaccination of infants, vaccination of adolescents, and vaccination of adults at high risk for infection. Recommendations to further enhance vaccination of adults at increased risk of HBV infection were published in 2006.

Strategy to Eliminate Hepatitis B Virus Transmission—United States

- Prevent perinatal HBV transmission
- Routine vaccination of all infants
- Vaccination of children in high-risk groups
- Vaccination of adolescents
- Vaccination of adults in high-risk groups

Hepatitis B Vaccine

Characteristics

A plasma-derived vaccine was licensed in the United States in 1981. It was produced from 22-nm HBsAg particles purified from the plasma of chronically infected humans. The vaccine was safe and effective but was not well accepted, possibly because of unsubstantiated fears of transmission of live HBV and other bloodborne pathogens (e.g., human immunodeficiency virus). This vaccine was removed from the U.S. market in 1992.

Recombinant hepatitis B vaccine was licensed in the United States in July 1986. A second, similar vaccine was licensed in August 1989.

Hepatitis B Vaccine

1965	Discovery of Australian antigen
1973	Successful HBV infection of chimpanzees
1981	Licensure of plasma-derived vaccine
1986	Licensure of recombinant vaccine
1991	Universal infant vaccination
1996	Universal adolescent vaccination

Hepatitis B Vaccine

- Composition: Recombinant HBsAg
- Efficacy: 95% (Range, 80%-100%)
- Duration of Immunity: at least 20 years
- Schedule: 3 Doses
- Booster doses not routinely recommended

Hepatitis B Vaccine Formulations

- Recombivax HB (Merck)
  - 5 mcg/0.5 mL (pediatric)
  - 10 mcg/1 mL (adult)
  - 40 mcg/1 mL (dialysis)
- Engerix-B (GSK)
  - 10 mcg/0.5 mL (pediatric)
  - 20 mcg/1 mL (adult)

Recombinant vaccine is produced by inserting a plasmid containing the gene for HBsAg into common baker's yeast (*Saccharomyces cerevisiae*). Yeast cells then produce HBsAg, which is harvested and purified. The recombinant vaccine contains more than 95% HBsAg protein (5 to 40 mcg/mL); yeast-derived proteins may constitute up to 5% of the final product, but no yeast DNA is detectable in the vaccine. HBV infection cannot result from use of the recombinant vaccine, since no potentially infectious viral DNA or complete viral particles are produced in the recombinant system. Vaccine HBsAg is adsorbed to aluminum hydroxide.

Hepatitis B vaccine is produced by two manufacturers in the United States, Merck (Recombivax HB) and GlaxoSmithKline Pharmaceuticals (Engerix-B). Both vaccines are available in both pediatric and adult formulations. Although the antigen content of the vaccines differs, vaccines made by different manufacturers are interchangeable, except for the two-dose schedule for adolescents aged 11 through 15 years. Only Merck vaccine is approved for this schedule. Providers must always follow the manufacturer's dosage recommendations.

Both the pediatric and adult formulations of Recombivax HB are approved for use in any age group. For example, the adult formulation of Recombivax HB may be used in children (0.5 mL) and adolescents (0.5 mL). However, pediatric Engerix-B is approved for use only in children and adolescents younger than 20 years of age. The adult formulation of Engerix-B is not approved for use in infants and children but may be used in both adolescents (11 through 19 years of age) and adults.

Engerix-B contains aluminum hydroxide as an adjuvant. It does not contain thimerosal as a preservative but contains a trace of thimerosal as residual from the manufacturing process. The vaccine is supplied in single-dose vials and syringes. Recombivax HB contains aluminum hydroxyphosphate sulfate as an adjuvant. None of the formulations of Recombivax HB contain thimerosal or any other preservative. The vaccine is supplied in single-dose vials.

Immunogenicity and Vaccine Efficacy

After three intramuscular doses of hepatitis B vaccine, more than 90% of healthy adults and more than 95% of infants, children, and adolescents (from birth to 19 years of age) develop adequate antibody responses. However, there is an age-specific decline in immunogenicity. After age 40 years, approximately 90% of recipients respond to a three-dose series, and by 60 years, only 75% of vaccinees develop

protective antibody titers. The proportion of recipients who respond to each dose varies by age (see table).

Protection* by Age Group and Dose

Dose	Infants†	Teens and Adults§
1	16% - 40%	20% - 30%
2	80% - 95%	75% - 80%
3	98% - 100%	90% - 95%

*Anti-HBs antibody titer of 10 mIU/mL or higher

†Preterm infants less than 2kg have been shown to respond to vaccination less often

§Factors that may lower vaccine response rates are age 40 years or older, male gender, smoking, obesity, and immune deficiency

The vaccine is 80% to 100% effective in preventing infection or clinical hepatitis in those who receive the complete course of vaccine. Larger vaccine doses (2 to 4 times the normal adult dose) or an increased number of doses are required to induce protective antibody in a high proportion of hemodialysis patients and may also be necessary in other immunocompromised persons.

The recommended dosage of vaccine differs depending on the age of the recipient and type of vaccine (see table). Hemodialysis patients should receive a 40-mcg dose in a series of three or four doses. Recombivax HB has a special dialysis patient formulation that contains 40 mcg/mL.

Recommended doses of currently licensed formulations of hepatitis B vaccine, by age group and vaccine type

	Single-Antigen Vaccine				Combination Vaccine					
	Recombivax HB		Engerix-B		Comvax		Pediarix		Twinrix	
Age Group	Dose (µg)*	Volume (mL)	Dose (µg)*	Volume (mL)	Dose (µg)*	Volume (mL)	Dose (µg)*	Volume (mL)	Dose (µg)*	Volume (mL)
Infants (<1 yr)	5	0.5	10	0.5	5	0.5	10	0.5	N/A**	N/A
Children (1-10 yrs)	5	0.5	10	0.5	5	0.5	10	0.5	N/A	N/A
Adolescents										
11-15 yrs	10†	1.0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
11-19 yrs	5	0.5	10	0.5	N/A	N/A	N/A	N/A	N/A	N/A
Adults (≥20 yrs)	10	1.0	20	1.0	N/A	N/A	N/A	N/A	20	1.0
Hemodialysis patients and other immunocompromised persons										
<20 yrs§	5	0.5	10	0.5	N/A	N/A	N/A	N/A	N/A	N/A
≥20 yrs	40¶	1.0	40‡	2.0	N/A	N/A	N/A	N/A	N/A	N/A

* Recombinant hepatitis B surface antigen protein dose.
† Adult formulation administered on a 2-dose schedule.
§ Higher doses might be more immunogenic, but no specific recommendations have been made.
¶ Dialysis formulation administered on a 3-dose schedule at 0, 1, and 6 months.
‡ Two 1.0 mL doses administered at one site, on a 4-dose schedule at 0, 1, 2, and 6 months.
** Not applicable.

Hepatitis B Vaccine
Long-Term Efficacy

- Immunologic memory established following vaccination
- Exposure to HBV results in anamnestic anti-HBs response
- Chronic infection rarely documented among vaccine responders

Hepatitis B Vaccine

Routine booster doses are NOT routinely recommended for any group

Hepatitis B Vaccine
Routine Infant Schedule

Dose	Usual Age	Minimum Interval
Primary 1	Birth	- - -
Primary 2	1- 2 months	4 weeks
Primary 3	6-18 months*	8 weeks**

* infants who mothers are HBsAg+ or whose HBsAg status is unknown should receive the third dose at 6 months of age
** at least 16 weeks after the first dose

The deltoid muscle is the recommended site for hepatitis B vaccination in adults and children, while the anterolateral thigh is recommended for infants and neonates. Immunogenicity of vaccine in adults is lower when injections are given in the gluteus. Hepatitis B vaccine should be administered to infants using a needle of at least 7/8 inch length and to older children and adults of at least 1 inch length. Hepatitis B vaccine administered by any route or site other than intramuscularly in the anterolateral thigh or deltoid muscle should not be counted as valid and should be repeated unless serologic testing indicates that an adequate response has been achieved.

Available data show that vaccine-induced antibody levels decline with time. However, immune memory remains intact for more than 20 years following immunization, and both adults and children with declining antibody levels are still protected against significant HBV infection (i.e., clinical disease, HBsAg antigenemia, or significant elevation of liver enzymes). Exposure to HBV results in an anamnestic anti-HBs response that prevents clinically significant HBV infection. Chronic HBV infection has only rarely been documented among vaccine responders.

For adults and children with normal immune status, booster doses of vaccine are not recommended. Routine serologic testing to assess immune status of vaccinees is not recommended. The need for booster doses after longer intervals will continue to be assessed as additional information becomes available.

For hemodialysis patients, the need for booster doses should be assessed by annual testing of vaccinees for antibody levels, and booster doses should be provided when antibody levels decline below 10 mIU/mL.

Vaccination Schedule and Use

Infants and Children

Hepatitis B vaccination is recommended for all infants soon after birth and before hospital discharge. Infants and children younger than 11 years of age should receive 0.5 mL (5 mcg) of pediatric or adult formulation Recombivax HB (Merck) or 0.5 mL (10 mcg) of pediatric Engerix-B (GlaxoSmithKline). Primary vaccination consists of three intramuscular doses of vaccine. The usual schedule is 0, 1 to 2, and 6 to 18 months. Infants whose mothers are HBsAg positive or whose HBsAg status is unknown should receive the last (third or fourth) dose by 6 months of age (12 to 15 months if Comvax is used).

Because the highest titers of anti-HBs are achieved when the last two doses of vaccine are spaced at least 4 months apart, schedules that achieve this spacing are preferable.

However, schedules with 2-month intervals between doses, which conform to schedules for other childhood vaccines, have been shown to produce good antibody responses and may be appropriate in populations in which it is difficult to ensure that infants will be brought back for all their vaccinations. However, the third dose must be administered at least 8 weeks after the second dose, and should follow the first dose by at least 16 weeks. For infants, the third dose should not be given earlier than 24 weeks of age. It is not necessary to add doses or restart the series if the interval between doses is longer than recommended.

Third Dose of Hepatitis B Vaccine

- Minimum of 8 weeks after second dose, and
- At least 16 weeks after first dose, and
- For infants, at least 24 weeks of age

Preterm infants born to HBsAg-positive women and women with unknown HBsAg status must receive immunoprophylaxis with hepatitis B vaccine and hepatitis B immune globulin (HBIG) within 12 hours of birth. See the section on Postexposure Prophylaxis for additional information. Preterm infants with low birthweight (i.e., less than 2,000 grams) have a decreased response to hepatitis B vaccine administered before 1 month of age. However, by chronologic age 1 month, preterm infants, regardless of initial birthweight or gestational age, are as likely to respond as adequately as full-term infants. Preterm infants of low birthweight whose mothers are HBsAg negative can receive the first dose of the hepatitis B vaccine series at chronologic age 1 month. Preterm infants discharged from the hospital before chronologic age 1 month can also be administered hepatitis B vaccine at discharge if they are medically stable and have gained weight consistently. The full recommended dose should be used. Divided or reduced doses are not recommended.

Preterm Infants

- Birth dose and HBIG if mother HBsAg positive
- Preterm infants <2,000 grams have a decreased response to vaccine administered before 1 month of age
- Delay first dose until chronologic age 1 month if mother HBsAg negative

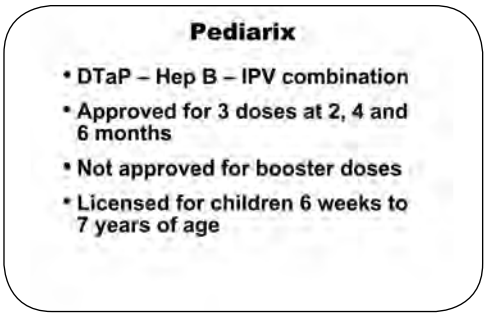
Comvax

Hepatitis B vaccine is available in combination with *Haemophilus influenzae* type b (Hib) vaccine as Comvax (Merck). Each dose of Comvax contains 7.5 mcg of PRP-OMP Hib vaccine (PedvaxHIB), and 5 mcg of hepatitis B surface antigen. The dose of hepatitis B surface antigen is the same as that contained in Merck's pediatric formulation. The immunogenicity of the combination vaccine is equivalent to that of the individual antigens administered at separate sites.

COMVAX

- Hepatitis B-Hib combination
- Use when either antigen is indicated
- Cannot use before 6 weeks of age
- May be used in infants whose mothers are HBsAg positive or status is unknown

Comvax is licensed for use at 2, 4, and 12 through 15 months of age. It may be used whenever either antigen is indicated and the other antigen is not contraindicated. However, the vaccine must not be administered to infants younger than 6 weeks of age because of potential suppression of the immune response to the Hib component (see Chapter 6, *Haemophilus influenzae* type b, for more details). Comvax must not be used for doses at birth or 1 month of age for a child on a 0, 1, 6 month hepatitis B vaccine schedule. Although it is not labeled for this indication by FDA, ACIP recommends that Comvax may be used in infants whose mothers are HBsAg positive or whose HBsAg status is unknown.

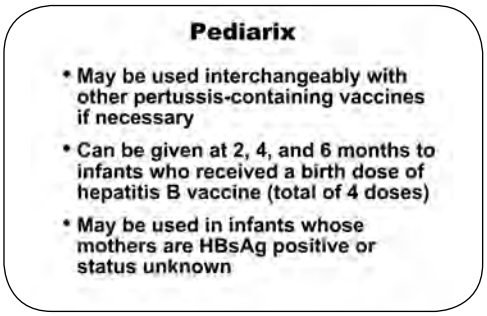


Pediarix

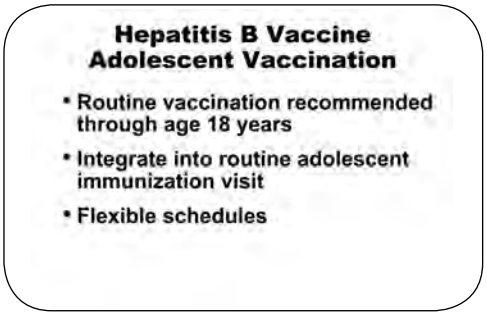
In 2002, the Food and Drug Administration approved Pediarix (GlaxoSmithKline), the first pentavalent (5-component) combination vaccine licensed in the United States. Pediarix contains DTaP (Infanrix), hepatitis B (Engerix-B), and inactivated polio vaccines. In prelicensure studies, the proportion of children who developed a protective level of antibody, and the titer of antibody, were at least as high among children receiving the vaccine antigens given together as Pediarix as among children who received separate vaccines.

The minimum age for the first dose of Pediarix is 6 weeks, so it cannot be used for the birth dose of the hepatitis B series. Pediarix is approved for the first three doses of the DTaP and IPV series, which are usually given at about 2, 4, and 6 months of age; it is not approved for fourth or fifth (booster) doses of the DTaP or IPV series. However, Pediarix is approved for use through 6 years of age. A child who is behind schedule can still receive Pediarix as long as it is given for doses 1, 2, or 3 of the series, and the child is younger than 7 years of age.

A dose of Pediarix inadvertently administered as the fourth or fifth dose of the DTaP or IPV series does not need to be repeated.



Pediarix may be used interchangeably with other pertussis-containing vaccines if necessary (although ACIP prefers the use of the same brand of DTaP for all doses of the series, if possible). It can be given at 2, 4, and 6 months to infants who received a birth dose of hepatitis B vaccine (total of 4 doses of hepatitis B vaccine). Although not labeled for this indication by FDA, Pediarix may be used in infants whose mothers are HBsAg positive or whose HBsAg status is unknown.



Adolescents

Routine hepatitis B vaccination is recommended for all children and adolescents through age 18 years. All children not previously vaccinated with hepatitis B vaccine should be vaccinated at 11 or 12 years of age with the age-appropriate dose of vaccine. When adolescent vaccination programs are being considered, local data should be considered to determine the ideal age group to vaccinate (i.e., preadolescents, young adolescents) to achieve the highest vaccination rates. The vaccination schedule should be flexible and should take into account the feasibility of delivering three doses of vaccine to this age group. Unvaccinated older adolescents should be vaccinated whenever possible. Those in groups at risk for HBV infection (e.g., Asian and Pacific Islanders, sexually active) should be identified and vaccinated in settings serving

this age group (i.e., schools, sexually transmitted disease clinics, detention facilities, drug treatment centers).

Persons younger than 20 years of age should receive 0.5 mL (5 mcg) of pediatric or adult formulation Recombivax HB (Merck) or 0.5 mL (10 mcg) of pediatric formulation Engerix-B (GlaxoSmithKline). The adult formulation of Engerix-B may be used in adolescents, but the approved dose is 1 mL (20 mcg).

The usual schedule for adolescents is two doses separated by no less than 4 weeks, and a third dose 4 to 6 months after the second dose. If an accelerated schedule is needed, the minimum interval between the first two doses is 4 weeks, and the minimum interval between the second and third doses is 8 weeks. However, the first and third doses should be separated by no less than 16 weeks. Doses given at less than these minimum intervals should not be counted as part of the vaccination series.

In 1999, the Food and Drug Administration approved an alternative hepatitis B vaccination schedule for adolescents 11 through 15 years of age. This alternative schedule is for two 1.0-mL (10 mcg) doses of Recombivax HB separated by 4 to 6 months. Seroconversion rates and postvaccination anti-HBs antibody titers were similar using this schedule or the standard schedule of three 5-mcg doses of RecombivaxHB. This alternative schedule is approved only for adolescents 11 through 15 years of age, and for Merck's hepatitis B vaccine. The 2-dose schedule should be completed by age 16 years.

Hepatitis B Vaccine
Adolescent and Adult Schedule

Dose	Usual Interval	Minimum Interval
Primary 1	---	---
Primary 2	1 month	4 weeks
Primary 3	5 months	8 weeks*

*third dose must be separated from first dose by at least 16 weeks

Alternative Adolescent Vaccination Schedule

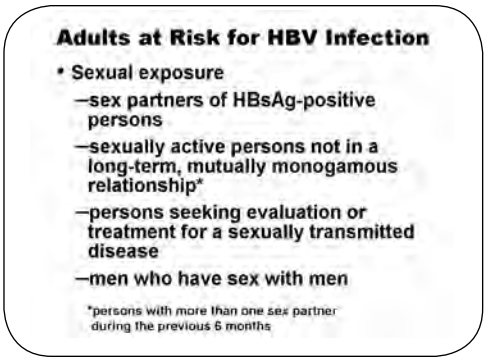
- Two 1.0-mL (10 mcg) doses of Recombivax HB separated by 4-6 months
- Approved only for adolescents 11-15 years of age
- Only applies to Merck hepatitis B vaccine

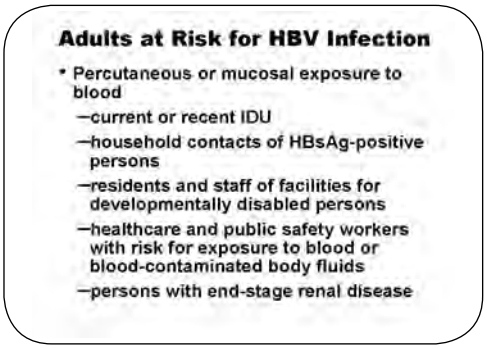
Adults (20 Years of Age and Older)

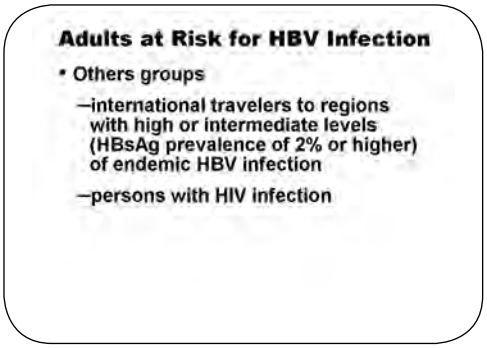
Routine preexposure vaccination should be considered for groups of adults who are at increased risk of HBV infection. Adults 20 years of age and older should receive 1 mL (10 mcg) of pediatric or adult formulation Recombivax HB (Merck) or 1 mL (20 mcg) of adult formulation Engerix-B (GlaxoSmithKline). The pediatric formulation of Engerix-B is not approved for use in adults.

The usual schedule for adults is two doses separated by no less than 4 weeks, and a third dose 4 to 6 months after the second dose. If an accelerated schedule is needed, the minimum interval between the first two doses is 4 weeks, and the minimum interval between the second and third doses is 8 weeks. However, the first and third doses should be separated by no less than 16 weeks. Doses given at less than these minimum intervals should not be counted as part of the vaccination series. It is not necessary to restart the series or add doses because of an extended interval between doses.

Hepatitis B







Hepatitis B vaccination is recommended for all unvaccinated adults at risk for HBV infection and for all adults requesting protection from HBV infection. Acknowledgment of a specific risk factor should not be a requirement for vaccination.

Persons at risk for infection by sexual exposure include sex partners of HBsAg-positive persons, sexually active persons who are not in a long-term, mutually monogamous relationship (e.g., persons with more than one sex partner during the previous 6 months), persons seeking evaluation or treatment for a sexually transmitted disease, and men who have sex with men.

Persons at risk for infection by percutaneous or mucosal exposure to blood include current or recent injection-drug users, household contacts of HBsAg-positive persons, residents and staff of facilities for developmentally disabled persons, healthcare and public safety workers with risk for exposure to blood or blood-contaminated body fluids and persons with end-stage renal disease, including predialysis, hemodialysis, peritoneal dialysis, and home dialysis patients. Persons with chronic liver disease are not at increased risk for HBV infection unless they have percutaneous or mucosal exposure to infectious blood or body fluids

Others groups at risk include international travelers to regions with high or intermediate levels (HBsAg prevalence of 2% or higher) of endemic HBV infection and persons with HIV infection.

In settings in which a high proportion of adults have risks for HBV infection (e.g., sexually transmitted disease/human immunodeficiency virus testing and treatment facilities, drug-abuse treatment and prevention settings, healthcare settings targeting services to IDUs, healthcare settings targeting services to MSM, and correctional facilities), ACIP recommends universal hepatitis B vaccination for all unvaccinated adults. In other primary care and specialty medical settings in which adults at risk for HBV infection receive care, healthcare providers should inform all patients about the health benefits of vaccination, including risks for HBV infection and persons for whom vaccination is recommended, and vaccinate adults who report risks for HBV infection and any adults requesting protection from HBV infection. To promote vaccination in all settings, healthcare providers should implement standing orders to identify adults recommended for hepatitis B vaccination and administer vaccination as part of routine clinical services, not require acknowledgment of an HBV infection risk factor for adults to receive vaccine, and use available reimbursement mechanisms to remove financial barriers to hepatitis B vaccination. Additional details about these strategies are available in the December 2006 ACIP statement on hepatitis B vaccine (see reference list).

Twinrix

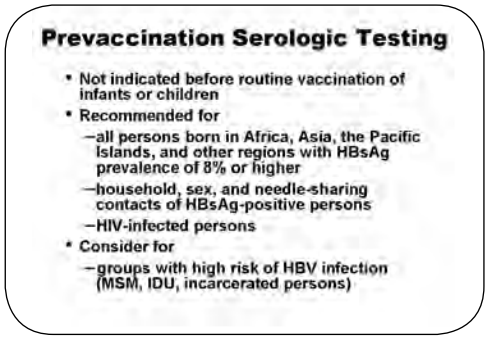
In 2001, the Food and Drug Administration approved a combination hepatitis A and hepatitis B vaccine (Twinrix, GlaxoSmithKline). Each dose of Twinrix contains 720 ELISA units of hepatitis A vaccine (equivalent to a pediatric dose of Havrix), and 20 mcg of hepatitis B surface antigen protein (equivalent to an adult dose of Engerix-B). The vaccine is administered in a three-dose series at 0, 1, and 6 months. Appropriate spacing of the doses must be maintained to assure long-term protection from both vaccines. The first and third doses of Twinrix should be separated by at least 6 months. The first and second doses should be separated by at least 4 weeks, and the second and third doses should be separated by at least 5 months. In 2007, the FDA approved an alternative Twinrix schedule of doses at 0, 7, and 21–31 days and a booster dose 12 months after the first dose. It is not necessary to restart the series or add doses if the interval between doses is longer than the recommended interval.

Twinrix is approved for persons aged 18 years and older, and can be used in persons in this age group with indications for both hepatitis A and hepatitis B vaccines. Because the hepatitis B component of Twinrix is equivalent to a standard dose of hepatitis B vaccine, the schedule is the same whether Twinrix or single-antigen hepatitis B vaccine is used. Single-antigen hepatitis A vaccine can be used to complete a series begun with Twinrix and vice versa. See the Chapter 7, Hepatitis A, for details.

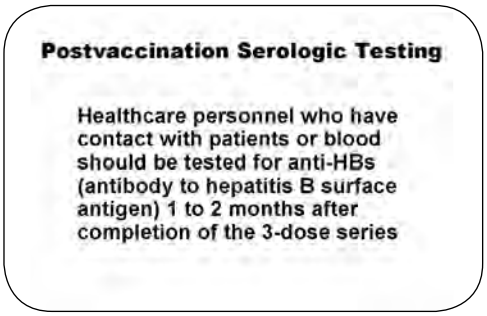
Serologic Testing of Vaccine Recipients

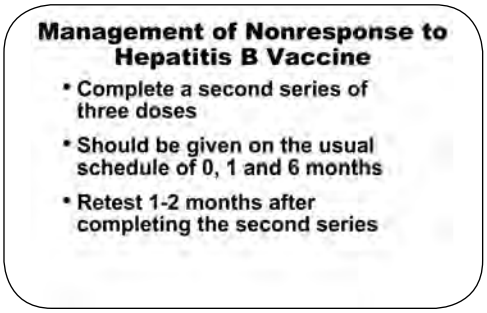
Prevaccination Serologic Testing

The decision to screen potential vaccine recipients for prior infection depends on the cost of vaccination, the cost of testing for susceptibility, and the expected prevalence of immune persons in the population being screened. Prevaccination testing is recommended for all foreign-born persons (including immigrants, refugees, asylum seekers, and internationally adopted children) born in Africa, Asia, the Pacific Islands, and other regions with high endemicity of HBV infection (HBsAg prevalence of 8% or higher); for household, sex, and needle-sharing contacts of HBsAg-positive persons; and for HIV-infected persons. Screening is usually cost-effective, and should be considered for groups with a high risk of HBV infection (prevalence of HBV markers 20% or higher), such as men who have sex with men, injection-drug users, and incarcerated persons. Screening is usually not cost-effective for groups with a low expected prevalence of HBV serologic markers, such as health professionals in their training years.









Serologic testing is not recommended before routine vaccination of infants and children.

Postvaccination Serologic Testing

Testing for immunity following vaccination is not recommended routinely but should be considered for persons whose subsequent management depends on knowledge of their immune status, such as chronic hemodialysis patients, other immunocompromised persons and persons with HIV infection. Testing is also recommended for sex partners of HBsAg-positive persons. When necessary, postvaccination testing should be performed 1 to 2 months after completion of the vaccine series.

Infants born to HBsAg-positive women should be tested for HBsAg and antibody to HBsAg (anti-HBs) after completion of at least 3 doses of the hepatitis B vaccine series, at age 9 through 18 months (generally at the next well-child visit). If HBsAg is not present and anti-HBs antibody is present, children can be considered to be protected.

Healthcare personnel who have contact with patients or blood and are at ongoing risk for injuries with sharp instruments or needlesticks should be routinely tested for antibody after 1 to 2 months after completion of the 3-dose series. However, a catch-up program of serologic testing for healthcare personnel vaccinated prior to December 1997 is not recommended. These persons should be tested as necessary if they have a significant exposure to HBV (see postexposure prophylaxis section below).

Routine postvaccination testing is not recommended for persons at low risk of exposure, such as public safety workers and healthcare personnel without direct patient contact.

Vaccine Nonresponse

Several factors have been associated with nonresponse to hepatitis B vaccine. These include vaccine factors (e.g., dose, schedule, injection site) and host factors. Older age (40 years and older), male sex, obesity, smoking, and chronic illness have been independently associated with nonresponse to hepatitis B vaccine. Further vaccination of persons who fail to respond to a primary vaccination series administered in the deltoid muscle produces adequate response in 15% to 25% of vaccinees after one additional dose and in 30% to 50% after three additional doses.

Persons who do not respond to the first series of hepatitis B vaccine should complete a second three-dose vaccine series. The second vaccine series should be given on the usual 0, 1, 6-month schedule. A 0, 1, 4-month accelerated schedule

may also be used. Revaccinated healthcare personnel and others for whom postvaccination serologic testing is recommended should be retested 1 to 2 months after completion of the second vaccine series.

Fewer than 5% of persons receiving six doses of hepatitis B vaccine administered by the appropriate schedule in the deltoid muscle fail to develop detectable anti-HBs antibody. Some persons who are anti-HBs negative following six doses may have a low level of antibody that is not detected by routine serologic testing ("hyporesponder"). However, one reason for persistent nonresponse to hepatitis B vaccine is that the person is chronically infected with HBV. Persons who fail to develop detectable anti-HBs after six doses should be tested for HBsAg. Persons who are found to be HBsAg positive should be counseled accordingly. Persons who fail to respond to two appropriately administered three-dose series, and who are HBsAg negative should be considered susceptible to HBV infection and should be counseled regarding precautions to prevent HBV infection and the need to obtain HBIG prophylaxis for any known or probable parenteral exposure to HBsAg-positive blood (see the postexposure prophylaxis table in this chapter).

It is difficult to interpret the meaning of a negative anti-HBs serologic response in a person who received hepatitis B in the past and was not tested after vaccination. Without postvaccination testing 1 to 2 months after completion of the series, it is not possible to determine if persons testing negative years after vaccination represent true vaccine failure (i.e., no initial response), or have anti-HBs antibody that has waned to below a level detectable by the test. The latter is the most likely explanation, because up to 60% of vaccinated people lose detectable antibody (but not protection) 9 to 15 years after vaccination.

One management option is to assume true vaccine failure and administer a second series to these persons. Serologic testing for anti-HBs antibody should be repeated 1 to 2 months after the sixth dose.

A second, probably less expensive option is to administer a single dose of hepatitis B vaccine and test for hepatitis B surface antibody in 4 to 6 weeks. If the person is anti-HBs antibody positive, this most likely indicates a booster response in a previous responder, and no further vaccination (or serologic testing) is needed. If the person is anti-HBs antibody negative after this "booster" dose, a second series should be completed (i.e., two more doses). If the person is still seronegative after six total doses, he or she should be managed as a nonresponder (see Postexposure Management, on the next page).

Persistent Nonresponse to Hepatitis B Vaccine

- <5% of vaccinees do not develop anti-HBsAg after 6 valid doses
- May be nonresponder or "hyporesponder"
- Check HBsAg status
- If exposed, treat as nonresponder with postexposure prophylaxis

Postexposure Management

Hepatitis B vaccine is recommended as part of the therapy used to prevent hepatitis B infection following exposure to HBV. Depending on the exposure circumstance, the hepatitis B vaccine series may be started at the same time as treatment with hepatitis B immune globulin (HBIG).

HBIG is prepared by cold ethanol fraction of plasma from selected donors with high anti-HBs titers; it contains an anti-HBs titer of at least 1:100,000, by RIA. It is used for passive immunization for accidental (percutaneous, mucous membrane) exposure, sexual exposure to an HBsAg-positive person, perinatal exposure of an infant, or household exposure of an infant younger than 12 months old to a primary caregiver with acute hepatitis B. Most candidates for HBIG are, by definition, in a high-risk category and should therefore be considered for vaccine as well.

Immune globulin (IG) is prepared by cold ethanol fractionation of pooled plasma and contains low titers of anti-HBs. Because titers are relatively low, IG has no valid current use for HBV disease unless hepatitis B immune globulin is unavailable.

Infants born to women who are HBsAg-positive (i.e., acutely or chronically infected with HBV) are at extremely high risk of HBV transmission and chronic HBV infection. Hepatitis B vaccination and one dose of HBIG administered within 24 hours after birth are 85%–95% effective in preventing both acute HBV infection and chronic infection. Hepatitis B vaccine administered alone beginning within 24 hours after birth is 70%–95% effective in preventing perinatal HBV infection.

HBIG (0.5 mL) should be given intramuscularly (IM), preferably within 12 hours of birth. Hepatitis B vaccine should be given IM in three doses. The first dose should be given at the same time as HBIG, but at a different site. If vaccine is not immediately available, the first injection should be given within 7 days of birth. The second and third doses should be given 1 to 2 months and 6 months, respectively, after the first. Testing for HBsAg and anti-HBs is recommended at 9 to 18 months of age (3 to 12 months after the third dose) to monitor the success of therapy. If the mother's HBsAg status is not known at the time of birth, the infant should be vaccinated within 12 hours of birth.

HBIG given at birth does not interfere with the administration of other vaccines administered at 2 months of age. Subsequent doses of hepatitis B vaccine do not interfere with the routine pediatric vaccine schedule.

Infants born to HBsAg-positive women and who weigh less than 2,000 grams at birth should receive postexposure

prophylaxis as described above. However, the initial vaccine dose (at birth) should not be counted in the 3-dose schedule. The next dose in the series should be administered when the infant is chronologic age 1 month. The third dose should be given 1 to 2 months after the second, and the fourth dose should be given at 6 months of age. These infants should be tested for HBsAg and anti-HBs at 9 to 18 months of age.

Women admitted for delivery whose HBsAg status is unknown should have blood drawn for testing. While test results are pending, the infant should receive the first dose of hepatitis B vaccine (without HBIG) within 12 hours of birth. If the mother is found to be HBsAg positive, the infant should receive HBIG as soon as possible but not later than 7 days of age. If the infant does not receive HBIG, it is important that the second dose of vaccine be administered at 1 or 2 months of age.

Preterm infants (less than 2,000 grams birthweight) whose mother's HBsAg status is unknown should receive hepatitis B vaccine within 12 hours of birth. If the maternal HBsAg status cannot be determined within 12 hours of birth HBIG should also be administered because of the immune response is less reliable in preterm infants weighing less than 2,000 grams. As described above, the vaccine dose administered at birth should not be counted as part of the series, and the infant should receive three additional doses beginning at age 1 month.The vaccine series should be completed by 6 months of age.

Few data are available on the use of Comvax or Pediarix in infants born to women who have acute or chronic infection with hepatitis B virus (i.e., HBsAg-positive). Neither vaccine is licensed for infants whose mothers are known to be acutely or chronically infected with HBV. However, ACIP has approved off-label use of Comvax and Pediarix in children whose mothers are HBsAg positive, or whose HBsAg status is unknown. Comvax and Pediarix should never be used in infants younger than 6 weeks of age. Either vaccine may be administered at the same time as other childhood vaccines given at 6 weeks of age or older.

After a percutaneous (needle stick, laceration, bite) or permucosal exposure that contains or might contain HBV, blood should be obtained from the person who was the source of the exposure to determine their HBsAg status. Management of the exposed person depends on the HBsAg status of the source and the vaccination and anti-HBs response status of the exposed person. Recommended postexposure prophylaxis is described in the table below.

Prevention of Perinatal Hepatitis B Virus Infection

- Begin treatment within 12 hours of birth
- Hepatitis B vaccine (first dose) and HBIG at different sites
- Complete vaccination series at 6 months of age
- Test for response at 9-18 months of age

Recommended Postexposure Prophylaxis for Occupational Exposure to Hepatitis B Virus

Vaccination and antibody status of exposed person*		Treatment		
		Source HBsAg** Positive	Source HBsAg** Negative	Source unknown or not available for testing
Unvaccinated		HBIG† X 1 and initiate HB vaccine series	Initiate HB vaccine series	Initiate HB vaccine series
Previously Vaccinated	Known Responder §	No treatment	No treatment	No treatment
	Known nonresponder ‡	HBIG X 1 and initiate revaccination or HBIG X 2 ††	No treatment	If known high-risk source, treat as if source were HBsAg positive
	Antibody response unknown	Test exposed person for anti-HBs ¶ – If adequate §, no treatment is necessary – If inadequate ‡, administer HBIG X 1 and vaccine booster	No treatment	Test exposed person for anti-HBs ¶ – If adequate §, no treatment is necessary – If inadequate ‡, administer vaccine booster and recheck titer in 1-2 months

* Persons who have previously been infected with HBV are immune to reinfection and do not require postexposure prophylaxis

** Hepatitis B surface antigen

† Hepatitis B immune globulin; dose is 0.06 mL/kg administered intramuscularly

§ A responder is a person with adequate levels of serum antibody to HBsAg (i.e., anti-HBs ≥10 mIU/mL)

‡ A nonresponder is a person with inadequate response to vaccination (i.e., serum anti-HBs <10 mIU/mL)

†† The option of giving one dose of HBIG and reinitiating the vaccine series is preferred for nonresponders who have not completed a second 3-dose vaccine series. For persons who previously completed a second vaccine series but failed to respond, two doses of HBIG are preferred.

¶ Antibody to HBsAg

Source: *MMWR* 2001; 50(RR-11) pg 22

Non-Occupational Exposure to an HBsAg-Positive Source

Persons who have written documentation of a complete hepatitis B vaccine series and who did not receive postvaccination testing should receive a single vaccine booster dose. Persons who are in the process of being vaccinated but who have not completed the vaccine series should receive the appropriate dose of HBIG and should complete the vaccine series. Unvaccinated persons should receive both HBIG and hepatitis B vaccine as soon as possible after exposure (preferably within 24 hours). Hepatitis B vaccine may be administered simultaneously with HBIG in a separate injection site.

Household, sex, and needle-sharing contacts of HBsAg-positive persons should be identified. Unvaccinated sex partners and household and needle-sharing contacts should be tested for susceptibility to HBV infection and should receive the first dose of hepatitis B vaccine immediately after collection of blood for serologic testing. Susceptible persons should complete the vaccine series using an age-appropriate vaccine dose and schedule. Persons who are not fully vaccinated should complete the vaccine series.

Non-Occupational Exposure to a Source with Unknown HBsAg Status

Persons with written documentation of a complete hepatitis B vaccine series require no further treatment. Persons who are not fully vaccinated should complete the vaccine series. Unvaccinated persons should receive the hepatitis B vaccine series with the first dose administered as soon as possible after exposure, preferably within 24 hours.

Contraindications and Precautions to Vaccination

A severe allergic reaction (anaphylaxis) to a vaccine component or following a prior dose of hepatitis B vaccine is a contraindication to further doses of vaccine. Such allergic reactions are rare.

Persons with moderate or severe acute illness should not be vaccinated until their condition improves. However, a minor illness, such as an upper respiratory infection, is not a contraindication to vaccination.

Specific studies of the safety of hepatitis B vaccine in pregnant women have not been performed. However, more than 20 years of experience with inadvertent administration to pregnant women have not identified vaccine safety issues for either the woman or the fetus. In contrast, if a pregnant woman acquires HBV infection, it may cause severe disease in the mother and chronic infection in the newborn baby. Therefore, hepatitis B vaccine may be administered to a pregnant woman who is otherwise eligible for it.

Hepatitis B vaccine does not contain live virus, so it may be used in persons with immunodeficiency. However, response to vaccination in such persons may be suboptimal.

Hepatitis B Vaccine
Contraindications and Precautions

- Severe allergic reaction to a vaccine component or following a prior dose
- Moderate or severe acute illness

Adverse Reactions Following Vaccination

The most common adverse reaction following hepatitis B vaccine is pain at the site of injection, reported in 13%–29% of adults and 3%–9% of children. Mild systemic complaints, such as fatigue, headache, and irritability, have been reported in 11% to 17% of adults and 0% to 20% of children. Fever (up to 99.9°F [37.7°C]) has been reported in 1% of adults and 0.4% to 6.4% of children. Serious systemic adverse reactions and allergic reactions are rarely reported following hepatitis B vaccine. There is no evidence that administration of hepatitis B vaccine at or shortly after birth increases the number of febrile episodes, sepsis evaluations, or allergic or neurologic events in the newborn period.

Hepatitis B vaccine has been alleged to cause or exacerbate multiple sclerosis (MS). A 2004 retrospective study in a

Hepatitis B Vaccine
Adverse Reactions

	Adults	Infants and Children
Pain at injection site	13%-29%	3%-9%
Mild systemic complaints (fatigue, headache)	11%-17%	0%-20%
Temperature ≤99.9°F (37.7°C)	1%	0.4%-6%
Severe systemic reactions	rare	rare

British population found a slight increase in risk of MS among hepatitis B vaccine recipients. However, large population-based studies have shown no association between receipt of hepatitis B vaccine and either the development of MS or exacerbation of the course of MS is persons already diagnosed with the disease.

Vaccine Storage and Handling

Hepatitis B vaccines should be stored refrigerated at 35°–46°F (2°–8°C), but not frozen. Exposure to freezing temperature destroys the potency of the vaccine.

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Human Papillomavirus

Human papillomavirus (HPV) is the most common sexually transmitted infection in the United States. The relationship of cervical cancer and sexual behavior was suspected for more than 100 years and was established by epidemiologic studies in the 1960s. In the early 1980s, cervical cancer cells were demonstrated to contain HPV DNA. Epidemiologic studies showing a consistent association between HPV and cervical cancer were published in the 1990s. The first vaccine to prevent infection with four types of HPV was licensed in 2006.

Human Papillomavirus

Human papillomaviruses are small, double-stranded DNA viruses that infect the epithelium. More than 100 HPV types have been identified; they are differentiated by the genetic sequence of the outer capsid protein L1. Most HPV types infect the cutaneous epithelium and cause common skin warts. About 40 types infect the mucosal epithelium; these are categorized according to their epidemiologic association with cervical cancer. Infection with low-risk, or nononcogenic types, such as types 6 and 11, can cause benign or low-grade cervical cell abnormalities, genital warts and laryngeal papillomas. High-risk, or oncogenic, HPV types act as carcinogens in the development of cervical cancer and other anogenital cancers. High-risk types (currently including types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 69, 73, 82) can cause low-grade cervical cell abnormalities, high-grade cervical cell abnormalities that are precursors to cancer, and anogenital cancers. High-risk HPV types are detected in 99% of cervical cancers. Type 16 is the cause of approximately 50% of cervical cancers worldwide, and types 16 and 18 together account for about 70% of cervical cancers. Infection with a high-risk HPV type is considered necessary for the development of cervical cancer, but by itself it is not sufficient to cause cancer because the vast majority of women with HPV infection do not develop cancer.

In addition to cervical cancer, HPV infection is also associated with anogenital cancers less common than cervical cancer, such as cancer of the vulva, vagina, penis and anus. The association of genital types of HPV with non-genital cancers is less well established, but studies support a role for these HPV types in a subset of oral cavity and pharyngeal cancers.

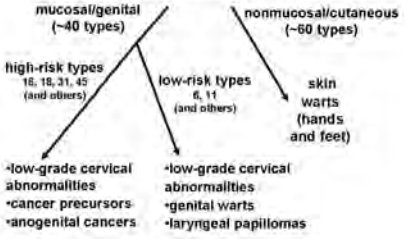
Pathogenesis

HPV infection occurs at the basal epithelium. Although the incidence of infection is high, most infections resolve spontaneously. A small proportion of infected persons become persistently infected; persistent infection is the most

Human Papillomavirus (HPV)

- Small DNA virus
- More than 100 types identified based on the genetic sequence of the outer capsid protein L1
- 40 types infect the mucosal epithelium

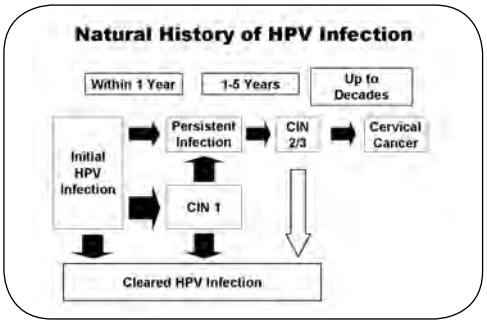
Human Papillomavirus Types and Disease Association



HPV-Associated Disease

Type	Women	Men
16/18	70% of cervical cancers	70% of anal cancers
	70% of anal/genital cancers	Transmission to women
6/11	90% of genital warts	90% of genital warts
	90% of RRP* lesions	90% of RRP lesions
		Transmission to women

* RRP = recurrent respiratory papillomatosis



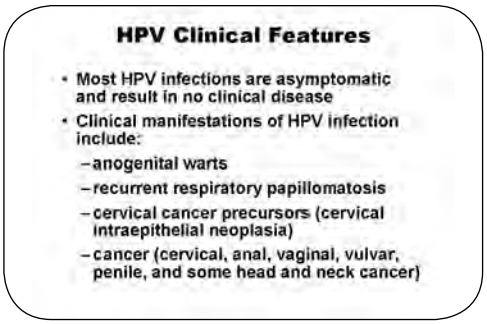
important risk factor for the development of cervical cancer precursor lesions. The most common clinically significant manifestation of persistent genital HPV infection is cervical intraepithelial neoplasia, or CIN. Within a few years of infection, low-grade CIN—called CIN 1—may develop, which may spontaneously resolve and the infection clear.

Persistent HPV infection, however, may progress directly to high-grade CIN, called CIN2 or CIN3. High-grade abnormalities are at risk of progression to cancer and so are considered cancer precursors. A small proportion of high-grade abnormalities spontaneously regress. If left undetected and untreated, years or decades later CIN2 or 3 can progress to cervical cancer.

Infection with one type of HPV does not prevent infection with another type. Of persons infected with mucosal HPV, 5% to 30% are infected with multiple types of the virus.

Clinical Features

Most HPV infections are asymptomatic and result in no clinical disease. Clinical manifestations of HPV infection include anogenital warts, recurrent respiratory papillomatosis, cervical cancer precursors (cervical intraepithelial neoplasia), and cancers, including cervical, anal, vaginal, vulvar, penile, and some head and neck cancer.



Laboratory Diagnosis

HPV has not been isolated in culture. Infection is identified by detection of HPV DNA from clinical samples. Assays for HPV detection differ considerably in their sensitivity and type specificity, and detection is also affected by the anatomic region sampled as well as the method of specimen collection.

Currently, only the Digene Hybrid Capture® 2 (hc2) High-Risk HPV DNA Test is approved by the Food and Drug Administration for clinical use The hc2 uses liquid nucleic acid hybridization and detects 13 high-risk types (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68). Results are reported as positive or negative and are not type-specific. The hc2 test is approved for triage of women with equivocal Papanicolaou (Pap) test results (ASC-US, atypical cells of undetermined significance) and in combination with the Pap test for cervical cancer screening in women 30 years of age and older. The test is not clinically indicated nor approved for use in men.

Epidemiologic and basic research studies of HPV generally use nucleic acid amplification methods that generate type-specific results. The PCR assays used most commonly in epidemiologic studies target genetically conserved regions in the L1 gene.

The most frequently used HPV serologic assays are VLP-based enzyme immunoassays. However, laboratory reagents used for these assays are not standardized and there are no standards for setting a threshold for a positive result.

Medical Management

There is no specific treatment for HPV infection. Medical management depends on treatment of the specific clinical manifestation of the infection (such as genital warts or abnormal cervical cell cytology).

Epidemiology

Occurrence

HPV infection occurs throughout the world.

Reservoir

Viruses in the papillomavirus family affect other species (notably rabbits and cows). However, humans are the only natural reservoir of HPV.

Transmission

HPV is transmitted by direct contact, usually sexual, with an infected person. Transmission occurs most frequently with sexual intercourse but can occur following nonpenetrative sexual activity.

Studies of newly acquired HPV infection demonstrate that infection occurs soon after onset of sexual activity. In a prospective study of college women, the cumulative incidence of infection was 40% by 24 months after first sexual intercourse. HPV 16 accounted for 10.4% of infections.

Genital HPV infection also may be transmitted by nonsexual routes, but this appears to be uncommon. Nonsexual routes of genital HPV transmission include transmission from a woman to a newborn infant at the time of birth.

Temporal Pattern

There is no known seasonal variation in HPV infection.

Communicability

HPV is presumably communicable during the acute infection and during persistent infection. This issue is difficult to study because of the inability to culture the virus. Communicability can presumed to be high because of the large number of new infections estimated to occur each year.

HPV Epidemiology

• Reservoir	Human
• Transmission	Direct contact, usually sexual
• Temporal pattern	None
• Communicability	Presumed to be high

HPV Disease Burden in the United States

- Anogenital HPV is the most common sexually transmitted infection in the US
  - –estimated 20 million currently infected
  - –6.2 million new infections/year
- Common among adolescents and young adults
- More than 80% of sexually active women will have been infected by age 50
- Infection also common in men

Cervical Cancer Disease Burden In the United States

- The American Cancer Society estimates that in 2008
  - –11,070 new cervical cancer cases
  - –3,870 cervical cancer deaths
- Almost 100% of these cervical cancer cases will be caused by one of the 40 HPV types that infect the mucosa

Risk Factors

Risk factors for HPV infection are related to sexual behavior, including the number of sex partners, lifetime history of sex partners, and the partners' sexual history. Most studies suggest that young age (less than 25 years) is a risk factor for infection. Results of epidemiologic studies are less consistent for other risk factors, including young age at sexual initiation, inconsistent condom use, number of pregnancies, genetic factors, smoking, lack of circumcision of male partner, and oral contraceptive use

Disease Burden in the United States

Anogenital HPV infection is believed to be the most common sexually transmitted infection in the United States. An estimated 20 million persons are currently infected, and an estimated 6.2 million new HPV infections occur annually. HPV infection is common among adolescents and young adults. Prevalence among adolescent girls is as high as 64%. Up to 75% of new infections occur among persons 15–24 years of age. Modeling estimates suggest that more than 80% of sexually active women will have been infected by age 50.

HPV infection is also common in men. Among heterosexual men in clinic-based studies, prevalence of genital HPV infection is often greater than 20%. Prevalence is highly dependent on the anatomic sites sampled and method of specimen collection.

The two most common types of cervical cancer worldwide, squamous cell carcinoma followed by adenocarcinoma, are both caused by HPV. The American Cancer Society estimates that in 2008 about 11,070 new cases of cervical cancer will be diagnosed in the United States. Approximately 3,870 women will die as a result of cervical cancer. HPV is believed to be responsible for nearly all of these cases of cervical cancer. HPV types 16 and 18 are associated with 70% of these cancers.

In addition to cervical cancer, HPV is believed to be responsible for 90% of anal cancers, 40% of vulvar, vaginal, or penile cancers, and 12% of oral and pharyngeal cancers.

Population-based estimates, primarily from clinics treating persons with sexually transmitted infections, indicate that about 1% of the sexually active adolescent and adult population in the United States have clinically apparent genital warts. More than 90% of cases of anogenital warts are associated with the low-risk HPV types 6 and 11.

About 4 billion dollars are spent annually on management of sequelae of HPV infections, primarily for the management of abnormal cervical cytology and treatment of cervical neoplasia. This exceeds the economic burden of any

other sexually transmitted infection except human immunodeficiency virus.

Prevention

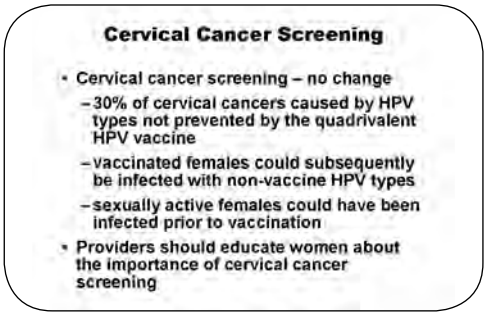
HPV Infection

HPV transmission can be reduced but not eliminated with the use of physical barriers such as condoms. Recent studies demonstrated a significant reduction in HPV infection among young women after initiation of sexual activity when their partners used condoms consistently and correctly. Abstaining from sexual activity (i.e., refraining from any genital contact with another individual) is the surest way to prevent genital HPV infection. For those who choose to be sexually active, a monogamous relationship with an uninfected partner is the strategy most likely to prevent future genital HPV infections.

Cervical Cancer Screening

Most cases and deaths from cervical cancer can be prevented through detection of precancerous changes within the cervix by cervical cytology using the Pap test. Currently available Pap test screening can be done by a conventional Pap or a liquid-based cytology. CDC does not issue recommendations for cervical cancer screening, but various professional groups have published recommendations. The American College of Obstetricians and Gynecologists (ACOG), the American Cancer Society (ACS), and the U.S. Preventive Services Task Force (USPSTF) guidelines recommend that all women should have a Pap test for cervical cancer screening within 3 years of beginning sexual activity or by age 21, whichever occurs first. While the USPSTF recommends a conventional Pap test at least every 3 years regardless of age, ACS and ACOG recommend annual or biennial screening of women younger than age 30, depending on use of conventional or liquid–based cytology. According to these national organizations, women over age 30 with three normal consecutive Pap tests should be screened every 2 to 3 years.

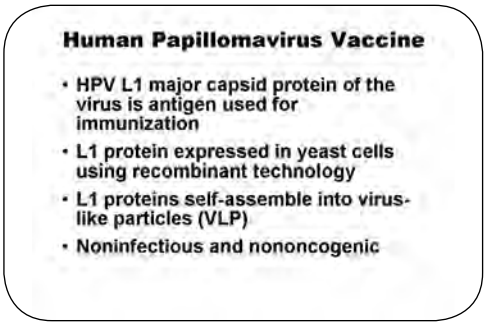
The use of HPV vaccine does not eliminate the need for continued Pap test screening, since 30% of cervical cancers are caused by HPV types not included in the vaccine.

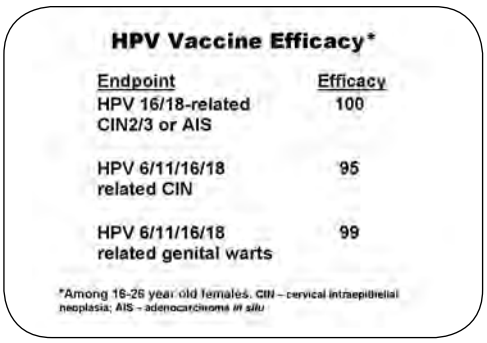


Human Papillomavirus Vaccine

Characteristics

The currently licensed vaccine is a quadrivalent HPV vaccine (Gardasil, Merck) approved by the Food and Drug Administration in June 2006. The vaccine antigen is the L1 major capsid protein of HPV, produced by using recombinant DNA technology. The L1 protein is expressed





in *Saccharomyces cerevisiae* (yeast) cells, and the protein self-assembles into noninfectious, nononcogenic virus-like-particles (VLP). Each 0.5-mL dose contains 20 µg HPV 6 L1 protein, 40 µg HPV 11 L1 protein, 40 µg HPV 16 L1 protein, and 20 µg HPV 18 L1 protein. The VLPs are adsorbed on 225 µg alum adjuvant. The vaccine also includes sodium chloride, L-histidine, polysorbate 80, sodium borate, and water for injection. The quadrivalent HPV vaccine contains no thimerosal or antibiotics. The vaccine is supplied in single-dose vials and syringes.

Immunogenicity and Vaccine Efficacy

The immunogenicity of the quadrivalent HPV vaccine has been measured by detection of IgG antibody to the HPV L1 by a type-specific immunoassay developed by the manufacturer. In all studies conducted to date, more than 99.5% of participants developed an antibody response to all four HPV types in the vaccine 1 month after completing the three-dose series. At that time interval, antibody titers against HPV types 6, 11, 16, and 18 were higher than those that developed after natural HPV infection.

There is no known serologic correlative of immunity and no known minimal titer determined to be protective. The high efficacy found in the clinical trials to date has precluded identification of a minimum protective antibody titer. Further follow-up of vaccinated cohorts may allow determination of serologic correlates of immunity in the future.

HPV vaccine has been found to have high efficacy for prevention of HPV vaccine type–related persistent infection, vaccine type–related CIN, CIN2/3, and external genital lesions in women 16–26 years of age. Clinical efficacy against cervical disease was determined in two double-blind, placebo-controlled trials, using various endpoints. Vaccine efficacy was 100% for prevention of HPV 16 or 18–related CIN 2/3 or adenocarcinoma in-situ (AIS). Efficacy against any CIN due to HPV 6, 11, 16, or 18 was 95%. Efficacy against HPV 6, 11, 16 or 18–related genital warts was 99%.

Although high efficacy among females without evidence of infection with vaccine HPV types was demonstrated in clinical trials, there was no evidence of efficacy against disease caused by vaccine types with which participants were infected at the time of vaccination. Participants infected with one or more vaccine HPV types prior to vaccination were protected against disease caused by the other vaccine types. However, prior infection with one HPV type did not diminish efficacy of the vaccine against other vaccine HPV types.

There is no evidence that the vaccine protects against disease due to non-vaccine HPV types or provides a therapeutic

effect against cervical disease or genital warts present at the time of vaccination.

A subset of participants in the phase II HPV vaccine study has been followed for 60 months post-dose 1 with no evidence of waning protection. Study populations will continue to be followed for any evidence of waning immunity.

HPV vaccine has been shown to be immunogenic and safe in males. However, no clinical efficacy data are available for males. These studies are in progress.

HPV Vaccine Efficacy

- High efficacy among females without evidence of infection with vaccine HPV types
- No evidence of efficacy against disease caused by vaccine types with which participants were infected at the time of vaccination
- Prior infection with one HPV type did not diminish efficacy of the vaccine against other vaccine HPV types

Vaccination Schedule and Use

Quadrivalent HPV vaccine is licensed by the Food and Drug Administration for use among females 9 through 26 years of age. The recommended age for routine vaccination in the United States is 11 or 12 years. The vaccine can be given as young as 9 years of age at the discretion of the clinician. The vaccine should be given at the same visit as other vaccines recommended for persons of this age (e.g., Tdap, meningococcal conjugate, hepatitis B).

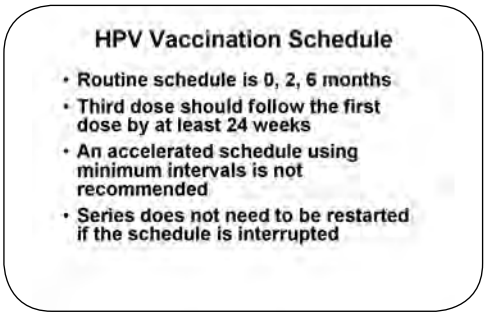
At the beginning of a vaccination program, there will be females older than 12 years of age who did not have the opportunity to receive vaccine at age 11 or 12 years. Catch-up vaccination is recommended for females 13 through 26 years of age who have not been previously vaccinated or who have not completed the full series. Ideally, vaccine should be administered before potential exposure to HPV through sexual contact; however, females who may have already been exposed to HPV should be vaccinated. Sexually active females who have not been infected with any of the HPV vaccine types will receive full benefit from vaccination. Vaccination will provide less benefit to females if they have already been infected with one or more of the four HPV vaccine types. However, it is not possible for a clinician to assess the extent to which sexually active females would benefit from vaccination, and the risk of HPV infection may continue as long as persons are sexually active. Pap testing or screening for HPV DNA or HPV antibody is not recommended prior to vaccination at any age.

Routine HPV Vaccination Recommendations

- ACIP recommends routine vaccination of females 11 or 12 years of age
- The vaccination series can be started as young as 9 years of age at the clinician's discretion
- Catch-up vaccination recommended for females 13 through 26 years of age

HPV vaccine is administered in a three-dose series of intramuscular injections. The second and third doses should be administered 2 and 6 months after the first dose. The third dose should follow the first dose by at least 24 weeks. An accelerated schedule for HPV vaccine is not recommended.

There is no maximum interval between doses. If the HPV vaccine schedule is interrupted, the vaccine series does



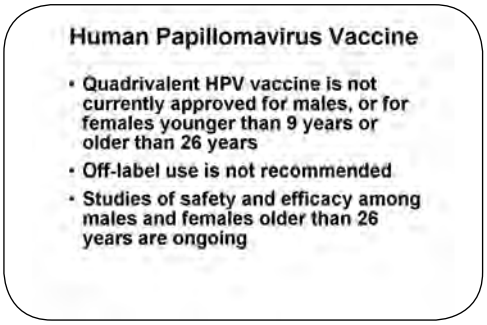
not need to be restarted. If the series is interrupted after the first dose, the second dose should be given as soon as possible, and the second and third doses should be separated by an interval of at least 12 weeks. If only the third dose is delayed, it should be administered as soon as possible.

HPV vaccine should be administered at the same visit as other age-appropriate vaccines, such as Tdap and quadrivalent meningococcal conjugate (MCV4) vaccines. Administering all indicated vaccines at a single visit increases the likelihood that adolescents and young adults will receive each of the vaccines on schedule. Each vaccine should be administered using a separate syringe at a different anatomic site.

The duration of protection from HPV vaccine is not known. Studies to investigate this issue are in progress. Booster doses are not recommended at this time.

HPV vaccine is not currently approved for use among males or among females younger than 9 years or older than 26 years of age. Use of the vaccine in males or females younger than 9 years or older than 26 years is not recommended. Studies among males and females older than 26 years of age are ongoing.

Females who have an equivocal or abnormal Pap test could be infected with any of more than 40 high-risk or low-risk genital HPV types. It is unlikely that such females would be infected with all four HPV vaccine types, and they may not be infected with any HPV vaccine type. Women younger than 27 years with a previously abnormal Pap test may be vaccinated. Women should be advised that data do not indicate the vaccine will have any therapeutic effect on existing HPV infection or cervical lesions.



Females who have a positive HPV DNA test (Hybrid Capture 2®) done in conjunction with a Pap test could be infected with any of 13 high-risk types. This assay does not identify specific HPV types, and testing for specific HPV types is not done routinely in clinical practice. Women younger than 27 years with a positive HPV DNA test may be vaccinated. HPV DNA testing is not a prerequisite for vaccination. Women should be advised that the vaccine will not have a therapeutic effect on existing HPV infection or cervical lesions.

A history of genital warts or clinically evident genital warts indicate infection with HPV, most often type 6 or 11. However, these females may be infected with HPV types other than the vaccine types, and therefore they may receive HPV vaccine if they are in the recommended age group. Women with a history of genital warts should be

advised that data do not indicate the vaccine will have any therapeutic effect on existing HPV infection or genital warts.

Because quadrivalent HPV vaccine is a subunit vaccine, it can be administered to females who are immunosuppressed because of disease or medications. However, the immune response and vaccine efficacy might be less than that in persons who are immunocompetent. Women who are breastfeeding may receive HPV vaccine.

Contraindications and Precautions to Vaccination

A severe allergic reaction (anaphylaxis) to a vaccine component or following a prior dose of HPV vaccine is a contraindication to receipt of HPV vaccine. A moderate or severe acute illness is a precaution to vaccination, and vaccination should be deferred until symptoms of the acute illness improve. A minor acute illness (e.g., diarrhea or mild upper respiratory tract infection, with or without fever) is not a reason to defer vaccination.

HPV vaccine is not recommended for use during pregnancy. The vaccine has not been associated with adverse pregnancy outcomes or with adverse effects on the developing fetus. However, data on vaccination during pregnancy are limited. Initiation of the vaccine series should be delayed until after completion of the pregnancy. If a woman is found to be pregnant after initiating the vaccination series, the remainder of the three-dose regimen should be delayed until after completion of the pregnancy. If a vaccine dose has been administered during pregnancy, no intervention is indicated. A vaccine in pregnancy registry has been established; patients and healthcare providers are urged to report any exposure to quadrivalent HPV vaccine during pregnancy by calling (800) 986-8999.

Adverse Reactions Following Vaccination

The most common adverse reactions reported during clinical trials of HPV vaccine were local reactions at the site of injection. These were most commonly pain (84%), swelling (25%), and erythema (25%). The majority of injection-site adverse experiences reported by recipients of quadrivalent HPV vaccine were mild to moderate in intensity. Fever was reported within 15 days of vaccination by 10% of vaccine recipients and 9% of placebo recipients. No serious adverse reactions have been reported.

A variety of systemic adverse reactions were reported by vaccine recipients, including nausea, dizziness, myalgia and

HPV Vaccine
Special Situations

- Vaccine can be administered
  - -equivocal or abnormal Pap Test
  - -positive HPV DNA test
  - -genital warts
  - -immunosuppression
  - -breastfeeding

HPV Vaccine
Contraindications and Precautions

- Contraindication
  - – severe allergic reaction to a vaccine component or following a prior dose
- Precaution
  - –moderate or severe acute illnesses (defer until symptoms improve)

Vaccination During Pregnancy
Provisional Recommendation

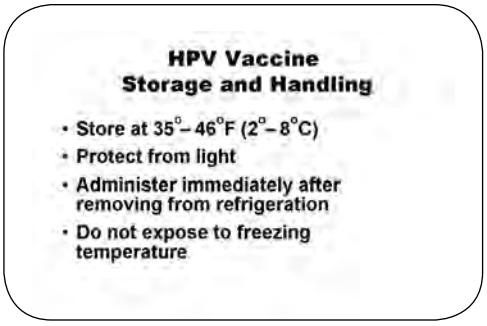
- Initiation of the vaccine series should be delayed until after completion of pregnancy
- If a woman is found to be pregnant after initiating the vaccination series, remaining doses should be delayed until after the pregnancy
- If a vaccine dose has been administered during pregnancy, there is no indication for intervention
- Women vaccinated during pregnancy should be reported to Merck registry (800.986.8999)

HPV Vaccine
Adverse Reactions

• Local reactions (pain, swelling)	84%
• Fever	10%*

- No serious adverse reactions reported

*similar to reports in placebo recipients (9%)



malaise. However, these symptoms occurred with equal frequency among both vaccine and placebo recipients.

Syncope has been reported among adolescents who received HPV and other vaccines recommended for this age group (Tdap, MCV). Recipients should always be seated during vaccine administration. Clinicians should consider observing persons for 15–20 minutes after vaccination.

Vaccine Storage and Handling

HPV vaccine should be stored continuously at 35°–46°F (2°–8°C) and should be protected from light. The vaccine should be removed from refrigeration immediately before administration. The vaccine must not be exposed to freezing temperature. Vaccine exposed to freezing temperature should never be administered.

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Human Papillomavirus

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Influenza

Influenza is a highly infectious viral illness. The name "influenza" originated in 15th century Italy, from an epidemic attributed to "influence of the stars." The first pandemic, or worldwide epidemic, that clearly fits the description of influenza was in 1580. At least four pandemics of influenza occurred in the 19th century, and three occurred in the 20th century. The pandemic of "Spanish" influenza in 1918–1919 caused an estimated 21 million deaths worldwide.

Smith, Andrews, and Laidlaw isolated influenza A virus in ferrets in 1933, and Francis isolated influenza B virus in 1936. In 1936, Burnet discovered that influenza virus could be grown in embryonated hens' eggs. This led to the study of the characteristics of the virus and the development of inactivated vaccines. The protective efficacy of these inactivated vaccines was determined in the 1950s. The first live attenuated influenza vaccine was licensed in 2003.

Influenza

- Highly infectious viral illness
- First pandemic in 1580
- At least 4 pandemics in 19th century
- Estimated 21 million deaths worldwide in pandemic of 1918-1919
- Virus first isolated in 1933

Influenza Virus

Influenza is a single-stranded, helically shaped, RNA virus of the orthomyxovirus family. Basic antigen types A, B, and C are determined by the nuclear material. Type A influenza has subtypes that are determined by the surface antigens hemagglutinin (H) and neuraminidase (N). Three types of hemagglutinin in humans (H1, H2, and H3) have a role in virus attachment to cells. Two types of neuraminidase (N1 and N2) have a role in virus penetration into cells.

Influenza A causes moderate to severe illness and affects all age groups. The virus infects humans and other animals. Influenza A viruses are perpetuated in nature by wild birds, predominantly waterfowl. Most of these viruses are not pathogenic to their natural hosts and do not change or evolve. Influenza B generally causes milder disease than type A and primarily affects children. Influenza B is more stable than influenza A, with less antigenic drift and consequent immunologic stability. It affects only humans. Influenza C is rarely reported as a cause of human illness, probably because most cases are subclinical. It has not been associated with epidemic disease.

The nomenclature to describe the type of influenza virus is expressed in this order: 1) virus type, 2) geographic site where it was first isolated, 3) strain number, 4) year of isolation, and 5) virus subtype.

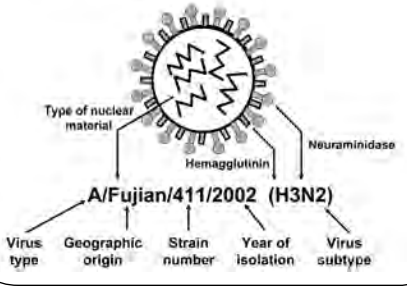
Influenza Virus

- Single-stranded RNA virus
- Orthomyxoviridae family
- 3 types: A, B, C
- Subtypes of type A determined by hemagglutinin and neuraminidase

Influenza Virus Strains

- Type A - moderate to severe illness
- all age groups
- humans and other animals
- Type B - milder disease
- primarily affects children
- humans only
- Type C - rarely reported in humans
- no epidemics

Influenza Virus



Antigenic Changes

Hemagglutinin and neuraminidase periodically change, apparently due to sequential evolution within immune or partially immune populations. Antigenic mutants emerge and are selected as the predominant virus to the extent that

Influenza Antigenic Changes

- Hemagglutinin and neuraminidase antigens change with time
- Changes occur as a result of point mutations in the virus gene, or due to exchange of a gene segment with another subtype of influenza virus
- Impact of antigenic changes depend on extent of change (more change usually means larger impact)

Influenza Antigenic Changes

- Antigenic Shift
  - —major change, new subtype
  - —caused by exchange of gene segments
  - —may result in pandemic
- Example of antigenic shift
  - —H2N2 virus circulated in 1957-1967
  - —H3N2 virus appeared in 1968 and completely replaced H2N2 virus

Influenza Antigenic Changes

- Antigenic Drift
  - —minor change, same subtype
  - —caused by point mutations in gene
  - —may result in epidemic
- Example of antigenic drift
  - —in 2002-2003, A/Panama/2007/99 (H3N2) virus was dominant
  - —A/Fujian/411/2002 (H3N2) appeared in late 2003 and caused widespread illness in 2003-2004

Influenza Type A Antigenic Shifts

Year	Subtype	Severity of Pandemic
1889	H3N2	Moderate
1918	H1N1	Severe
1957	H2N2	Severe
1968	H3N2	Moderate
1977	H1N1	Mild

they differ from the antecedent virus, which is suppressed by specific antibody arising in the population as a result of infection. This cycle repeats continuously. In interpandemic periods, mutants arise by serial point mutations in the RNA coding for hemagglutinin. At irregular intervals of 10 to 40 years, viruses showing major antigenic differences from prevalent subtypes appear and, because the population does not have protective antibody against these new antigens, cause pandemic disease in all age groups.

Antigenic shift is a major change in one or both surface antigens (H or N) that occurs at varying intervals. Antigenic shifts are probably due to genetic recombination (an exchange of a gene segment) between influenza A viruses, usually those that affect humans and birds. An antigenic shift may result in a worldwide pandemic if the virus is efficiently transmitted from person to person. The last major antigenic shift occurred in 1968 when H3N2 (Hong Kong) influenza appeared. It completely replaced the type A strain (H2N2, or Asian influenza) that had circulated throughout the world for the prior 10 years. There is concern among some influenza experts that the increasingly wide geographic distribution of a highly pathogenic avian virus (H5N1) could increase the chance of another antigenic shift. Although H5N1 virus is known to infect humans who are in contact with infected poultry, the virus is not efficiently transmitted from one human to another. Efficient person-to-person transmission is a necessary characteristic of an influenza virus with pandemic potential.

Antigenic drift is a minor change in surface antigens that results from point mutations in a gene segment. Antigenic drift may result in an epidemic, since the protection that remains from past exposures to similar viruses is incomplete. Drift occurs in all three types of influenza virus (A,B,C). For instance, during most of the 1997–1998 influenza season, A/Wuhan/359/95 (H3N2) was the predominant influenza strain isolated in the United States. A/Wuhan was a drifted distant relative of the 1968 Hong Kong H3N2 strain. In the last half of the 1997–1998 influenza season, a drifted variant of A/Wuhan appeared. This virus, named A/Sydney/5/97, was different enough from A/Wuhan (which had been included in the 1997–1998 vaccine) that the vaccine did not provide much protection. Both A/Wuhan and A/Sydney circulated late in the 1997–1998 influenza season. A/Sydney became the predominant strain during the 1998–1999 influenza season and was included in the 1998–1999 vaccine.

Since the late 19th century, four occurrences of antigenic shifts have led to major pandemics (1889–1891, 1918–1920, 1957–1958, and 1968–1969). A pandemic starts from a single focus and spreads along routes of travel. Typically, there are high attack rates involving all age groups, and mortality is usually markedly increased. Severity is gener-

ally not greater in the individual patient (except for the 1918–1919 strain), but because large numbers of persons are infected, the number, if not the proportion, of severe and fatal cases will be large. Onset may occur in any season of the year. Secondary and tertiary waves may occur every period of 1–2 years, usually in the winter.

Typically in an epidemic, influenza attack rates are lower than in pandemics. There is usually a rise in excess mortality. The major impact is observed in morbidity, with high attack rates and excess rates of hospitalization, especially for adults with respiratory disease. Absenteeism from work and school is high, and visits to healthcare providers increase. In the Northern Hemisphere, epidemics usually occur in late fall and continue through early spring. In the Southern Hemisphere, epidemics usually occur 6 months before or after those in the Northern Hemisphere.

Sporadic outbreaks can occasionally be localized to families, schools, and isolated communities.

Pathogenesis

Following respiratory transmission, the virus attaches to and penetrates respiratory epithelial cells in the trachea and bronchi. Viral replication occurs, which results in the destruction of the host cell. Viremia has rarely been documented. Virus is shed in respiratory secretions for 5–10 days.

Influenza Pathogenesis

- Respiratory transmission of virus
- Replication in respiratory epithelium with subsequent destruction of cells
- Viremia rarely documented
- Viral shedding in respiratory secretions for 5-10 days

Clinical Features

The incubation period for influenza is usually 2 days, but can vary from 1 to 4 days. The severity of influenza illness depends on the prior immunologic experience with antigenically related virus variants. In general, only about 50% of infected persons will develop the classic clinical symptoms of influenza.

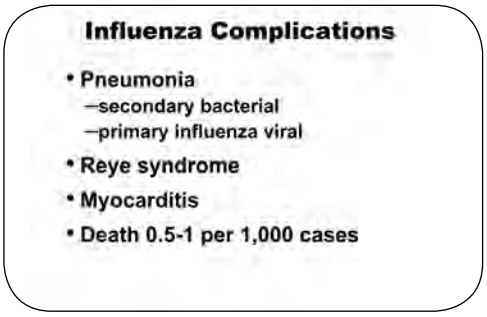
Influenza Clinical Features

- Incubation period 2 days (range 1-4 days)
- Severity of illness depends on prior experience with related variants
- Abrupt onset of fever, myalgia, sore throat, nonproductive cough, headache

"Classic" influenza disease is characterized by the abrupt onset of fever, myalgia, sore throat, nonproductive cough, and headache. The fever is usually 101°–102°F, and accompanied by prostration. The onset of fever is often so abrupt that the exact hour is recalled by the patient. Myalgias mainly affect the back muscles. Cough is believed to be a result of tracheal epithelial destruction. Additional symptoms may include rhinorrhea (runny nose), headache, substernal chest burning and ocular symptoms (e.g., eye pain and sensitivity to light).

Systemic symptoms and fever usually last from 2 to 3 days, rarely more than 5 days. They may be decreased by such medications as aspirin or acetaminophen. Aspirin should not be used for infants, children, or teenagers because they may be at risk for contracting Reye syndrome following an influenza infection. Recovery is usually rapid, but some

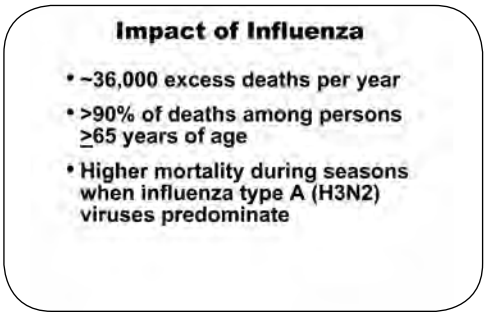
patients may have lingering depression and asthenia (lack of strength or energy) for several weeks.



Complications

The most frequent complication of influenza is pneumonia, most commonly secondary bacterial pneumonia (e.g., *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Staphylococcus aureus*). Primary influenza viral pneumonia is an uncommon complication with a high fatality rate. Reye syndrome is a complication that occurs almost exclusively in children taking aspirin, primarily in association with influenza B (or varicella zoster), and presents with severe vomiting and confusion, which may progress to coma due to swelling of the brain.

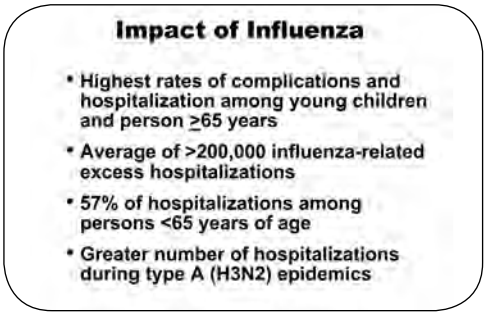
Other complications include myocarditis (inflammation of the heart) and worsening of chronic bronchitis and other chronic pulmonary diseases. Death is reported in 0.5–1 per 1,000 cases. The majority of deaths occur among persons 65 years of age and older.



Impact of Influenza

An increase in mortality typically accompanies an influenza epidemic. Increased mortality results not only from influenza and pneumonia but also from cardiopulmonary and other chronic diseases that can be exacerbated by influenza.

In a study of influenza epidemics, approximately 19,000 influenza-associated pulmonary and circulatory deaths per influenza season occurred during 1976–1990, compared with approximately 36,000 deaths during 1990–1999. Persons 65 years of age and older account for more than 90% of deaths attributed to pneumonia and influenza. In the United States, the number of influenza-associated deaths might be increasing, in part because the number of older persons is increasing. In addition, influenza seasons in which influenza A (H3N2) viruses predominate are associated with higher mortality.



The risk for complications and hospitalizations from influenza are higher among persons 65 years of age and older, young children, and persons of any age with certain underlying medical conditions. An average of more than 200,000 hospitalizations per year are related to influenza, more than 57% of which are among persons younger than 65 years. A greater number of hospitalizations occur during years that influenza A (H3N2) is predominant. In nursing homes, attack rates may be as high as 60%, with fatality rates as high as 30%. The cost of a severe epidemic has been estimated to be $12 billion.

Among children 0–4 years of age, hospitalization rates have varied from 100 per 100,000 healthy children to as high

as 500 per 100,000 for children with underlying medical conditions. Hospitalization rates for children 24 months of age and younger are comparable to rates for persons 65 and older. Children 24-59 months of age are at less risk of hospitalization from influenza than are younger children, but are at increased risk for influenza-associated clinic and emergency department visits.

Healthy children 5 through 18 years of age are not at increased risk of complications of influenza. However, children typically have the highest attack rates during community outbreaks of influenza. They also serve as a major source of transmission of influenza within communities. Influenza has a substantial impact among school-aged children and their contacts. These impacts include school absenteeism, medical care visits, and parental work loss. Studies have documented 5 to 7 influenza-related outpatient visits per 100 children annually, and these children frequently receive antibiotics.

An influenza pandemic could affect up to 200 million people and result in up to 400,000 deaths. The 1918–1919 influenza pandemic is believed to have resulted in the death of at least 500,000 Americans in less than a year. Planning for pandemic influenza is a critical component of public health preparedness activities and should be conducted by all local and state public health agencies. The federal pandemic plan is available on the Department of Health and Human Services website at http://www.hhs.gov/pandemicflu/plan/

Laboratory Diagnosis

The diagnosis of influenza is usually suspected on the basis of characteristic clinical findings, particularly if influenza has been reported in the community.

Virus can be isolated from throat and nasopharyngeal swabs obtained within 3 days of onset of illness. Culture is performed by inoculation of the amniotic or allantoic sac of chick embryos or certain cell cultures that support viral replication. A minimum of 48 hours is required to demonstrate virus, and 1 to 2 additional days to identify the virus type. As a result, culture is helpful in defining the etiology of local epidemics, but not in individual case management.

Serologic confirmation of influenza requires demonstration of a significant rise in influenza IgG. The acute-phase specimen should be taken less than 5 days from onset, and a convalescent specimen taken 10–21 days (preferably 21 days) following onset. Complement fixation (CF) and hemagglutination inhibition (HI) are the serologic tests most commonly used. The key test is HI, which depends on the ability of the virus to agglutinate human or chicken erythrocytes and inhibition of

Hospitalization Rates for Influenza By Age and Risk Group*

Age Group	Rate** (high-risk)	Rate** (not high-risk)
0-11 mos	1900	496-1038
1-2 yrs	800	186
3-4 yrs	320	86
5-14 yrs	92	41
15-44 yrs	56-110	23-25
45-64 yrs	392-635	13-23
≥65 yrs	399-518	125-228

* Data from several studies 1972 - 1995
** Hospitalizations per 100,000 population

Influenza Among School-Aged Children

- School-aged children
  - —typically have the highest attack rates during community outbreaks of influenza
  - —serve as a major source of transmission of influenza within communities

Influenza Diagnosis

- Clinical and epidemiological characteristics
- Isolation of influenza virus from clinical specimen (e.g., nasopharynx, throat, sputum)
- Significant rise in influenza IgG by serologic assay
- Direct antigen testing for type A virus

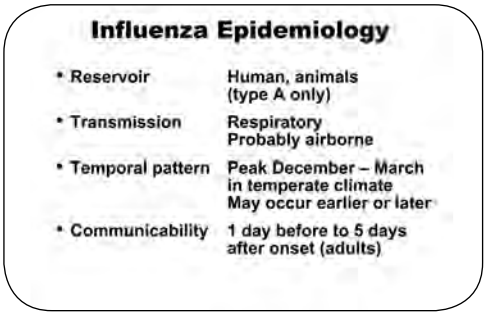
this process by specific antibody. Diagnosis requires at least a fourfold rise in antibody titer. Rapid diagnostic testing for influenza antigen permits those in office and clinic settings to assess the need for antiviral use in a more timely manner.

Details about the laboratory diagnosis of influenza are available on the CDC influenza website at http://www.cdc.gov/flu/professionals/diagnosis/index.htm

Epidemiology

Occurrence

Influenza occurs throughout the world.

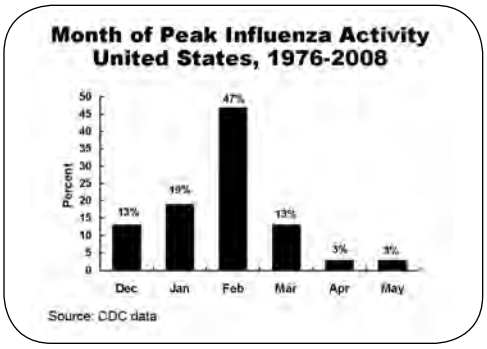


Reservoir

Humans are the only known reservoir of influenza types B and C. Influenza A may infect both humans and animals. There is no chronic carrier state.

Transmission

Influenza is primarily transmitted from person to person via large virus-laden droplets (particles more than 5 microns in diameter) that are generated when infected persons cough or sneeze. These large droplets can then settle on the mucosal surfaces of the upper respiratory tracts of susceptible persons who are near (within 3 feet) infected persons. Transmission may also occur through direct contact or indirect contact with respiratory secretions such as when touching surfaces contaminated with influenza virus and then touching the eyes, nose or mouth.



Temporal Pattern

Influenza activity peaks from December to March in temperate climates, but may occur earlier or later. During 1976–2008, peak influenza activity in the United States occurred most frequently in January (19% of seasons) and February (47% of seasons). However, peak influenza activity occurred in March, April, or May in 19% of seasons. Influenza occurs throughout the year in tropical areas.

Communicability

Adults can transmit influenza from the day before symptom onset to approximately 5 days after symptoms begin. Children can transmit influenza to others for 10 or more days.

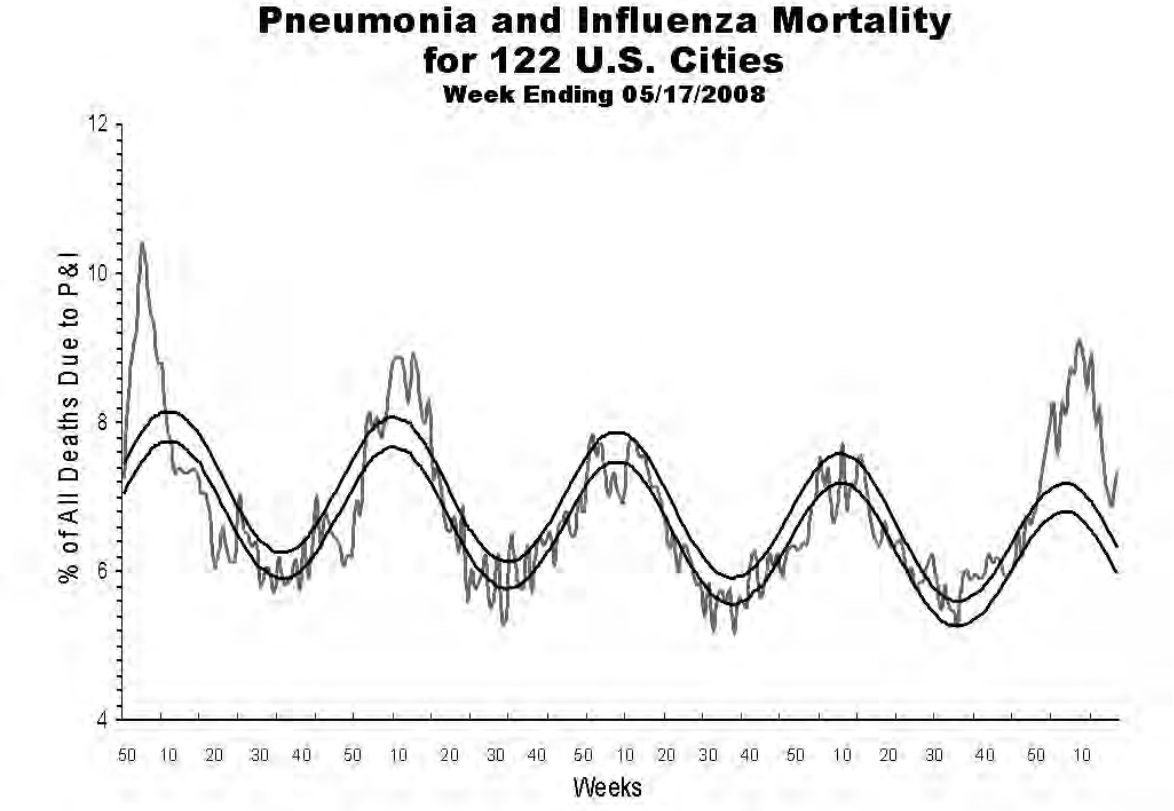
Secular Trends in the United States

There is a documented association between influenza and increased morbidity in high-risk adult populations.

Hospitalization for adults with high-risk medical conditions increases two- to fivefold during major epidemics.

The impact of influenza in the United States is quantified by measuring pneumonia and influenza (P and I) deaths. Death certificate data are collected from 122 U.S. cities with populations of more than 100,000 (total of approximately 70,000,000). P and I deaths include all deaths for which pneumonia is listed as a primary or underlying cause or for which influenza is listed on the death certificate.

An expected ratio of deaths due to P and I compared with all deaths for a given period of time is determined. The epidemic threshold for influenza seasons is generally estimated at 1.645 standard deviations above observed P and I deaths for the previous 5-year period excluding periods during influenza outbreaks. Influenza epidemic activity is signaled when the ratio of deaths due to P and I exceeds the threshold ratio for 2 consecutive weeks.



Influenza Vaccine

Characteristics

Two types of influenza vaccine are available in the United States. Trivalent inactivated influenza vaccine (TIV) has been available since the 1940s. TIV is administered by the intramuscular route and currently contains three inactivated

Influenza Vaccines

- Inactivated subunit (TIV)
  - –intramuscular
  - –trivalent
- Live attenuated vaccine (LAIV)
  - –intranasal
  - –trivalent

Transmission of LAIV Virus

- LAIV replicates in the nasopharyngeal mucosa
- Mean shedding of virus 7.6 days – longer in children
- One instance of transmission of vaccine virus documented in a child care setting
- Transmitted virus retained attenuated, cold-adapted, temperature-sensitive characteristics
- No transmission of LAIV reported in the U.S.

viruses: type A (H1N1), type A (H3N2), and type B. Only split-virus and subunit inactivated vaccines are available in the United States. Vaccine viruses are grown in chicken eggs, and the final product contains residual egg protein. The vaccine is available in both pediatric (0.25-mL dose) and adult (0.5-mL dose) formulations. TIV is available with thimerosal as a preservative (in multidose vials), and in reduced and preservative free formulations.

For the 2008–2009 influenza season four manufacturers provided TIV. Fluzone (sanofi pasteur) was available in multidose vials, in a thimerosal-free pediatric formulation (0.25 mL) in single-dose syringes, and in a thimerosal-free adult formulation in single-dose syringes and vials. Fluzone is the only TIV currently approved for use among children younger than 48 months. Fluvirin (Novartis) was available in multidose vials. Fluvirin is approved only for persons 4 years of age and older. Fluarix (GlaxoSmithKline) was available in a reduced-thimerosal ("preservative free") single-dose syringe for persons 18 years of age and older. FluLaval (GlaxoSmithKline) was available in a multidose vial for persons 18 years of age and older. Afluria (CSL Biotherapies) was available in a single-dose syringe and multidose vial for persons 18 years of age and older. All TIV supplied in multidose vials contains thimerosal as a preservative.

Live attenuated influenza vaccine (LAIV) was approved for use in the United States in 2003. It contains the same three influenza viruses as TIV. The viruses are cold-adapted, and replicate effectively in the mucosa of the nasopharynx. The vaccine viruses are grown in chicken eggs, and the final product contains residual egg protein. The vaccine is provided in a single-dose sprayer unit; half of the dose is sprayed into each nostril. LAIV does not contain thimerosal or any other preservative. LAIV is approved for use only in healthy, nonpregnant persons 2 through 49 years of age.

Vaccinated children can shed vaccine viruses in nasopharyngeal secretions for up to 3 weeks. One instance of transmission of vaccine virus to a contact has been documented. The transmitted virus retained its attenuated, cold-adapted, temperature-sensitive characteristics. The frequency of shedding of vaccine strains by persons 5–49 years of age has not been determined.

Immunogenicity and Vaccine Efficacy

TIV

For practical purposes, immunity following inactivated influenza vaccination is less than 1 year because of waning of vaccine-induced antibody and antigenic drift of circulating influenza viruses. Influenza vaccine efficacy varies by the similarity of the vaccine strain(s) to the circulating strain

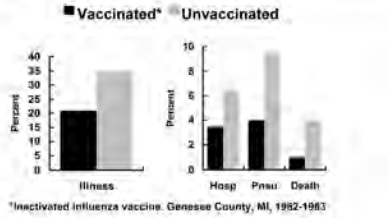
Inactivated Influenza Vaccine Efficacy

- 70%-90% effective among healthy persons <65 years of age
- 30%-40% effective among frail elderly persons
- 50%-60% effective in preventing hospitalization
- 80% effective in preventing death

and the age and health status of the recipient. Vaccines are effective in protecting up to 90% of healthy vaccinees younger than 65 years of age from illness when the vaccine strain is similar to the circulating strain. However, the vaccine is only 30%–40% effective in preventing illness among persons 65 years of age and older.

Although the vaccine is not highly effective in preventing clinical illness among the elderly, it is effective in preventing complications and death. Among elderly persons, the vaccine is 50%–60% effective in preventing hospitalization and 80% effective in preventing death. During a 1982–1983 influenza outbreak in Genesee County, Michigan, unvaccinated nursing home residents were four times more likely to die than were vaccinated residents.

Influenza and Complications Among Nursing Home Residents



*Inactivated influenza vaccine. Genesee County, MI, 1982-1983

LAIV

LAIV has been tested in groups of both healthy children and healthy adults. A randomized, double-blind, placebo-controlled trial among healthy children 60–84 months of age assessed the efficacy of the trivalent LAIV against culture-confirmed influenza during two influenza seasons. In year 1, when vaccine and circulating virus strains were well matched, efficacy was 87% against culture-confirmed influenza. In year 2, when the type A component was not well matched between vaccine and circulating virus strains, efficacy was also 87%. Other results from this trial included a 27% reduction in febrile otitis media and a 28% reduction in otitis media with concomitant antibiotic use. Receipt of LAIV also resulted in decreased fever and otitis media in vaccine recipients who developed influenza.

LAIV Efficacy in Healthy Children

- 87% effective against culture-confirmed influenza in children 5-7 years old
- 27% reduction in febrile otitis media (OM)
- 28% reduction in OM with accompanying antibiotic use
- Decreased fever and OM in vaccine recipients who developed influenza

A randomized, double-blind, placebo-controlled trial among 3,920 healthy working adults aged 18–49 years assessed several endpoints and documented reductions in illness, absenteeism, healthcare visits, and medication use during influenza outbreak periods. This study was conducted during the 1997–98 influenza season, when the vaccine and circulating type A strains were not well matched. This study did not include laboratory virus testing of cases. Three studies among children have demonstrated greater efficacy for LAIV compared to TIV. There is no evidence in adults that efficacy of LAIV is greater than that of TIV.

LAIV Efficacy in Healthy Adults

- 20% fewer severe febrile illness episodes
- 24% fewer febrile upper respiratory illness episodes
- 27% fewer lost work days due to febrile upper respiratory illness
- 18%-37% fewer days of healthcare provider visits due to febrile illness
- 41%-45% fewer days of antibiotic use

Vaccination Schedule and Use

TIV

Influenza activity peaks in temperate areas between late December and early March. TIV is most effective when it precedes exposure by no more than 2 to 4 months. It should be offered annually, beginning in September for routine patient visits. The optimal time for vaccination efforts is

Timing of Inactivated Influenza Vaccine Programs

- Actively target vaccine available in September and October to persons at increase risk of influenza complications, children <9 years, and healthcare personnel
- Vaccination of all other groups should begin in November
- Continue vaccinating through December and later, as long as vaccine is available

usually during October and November. In October vaccination in provider-based settings should start or continue for all patients,-both high risk and healthy-and extend through November. Vaccination of children aged 6 months through 8 years of age who are receiving vaccine for the first time should also begin in October, if not done earlier, because those children need a second dose 4 weeks after the initial dose. Organized vaccination campaigns should be scheduled no earlier than mid-October. Vaccine may be given up to and even after influenza activity is documented in a region. Although most influenza vaccination activities should be completed by December (particularly for high-risk groups), providers should continue to provide vaccine throughout influenza season.

One dose of TIV may be administered annually for persons 9 years of age or older. Children 6 months to 9 years of age receiving influenza vaccine for the first time should receive two doses administered at least 1 month apart.

Inactivated Influenza Vaccine Dosage, by Age Group – United States

Age Group	Dosage	Number of Doses	Route
6-35 months	0.25 mL	1* or 2	IM
3-8 years	0.50 mL	1* or 2	IM
≥9 years	0.50 mL	1	IM

*Only one dose is needed if the child received two doses of influenza vaccine during a previous influenza season.

Inactivated Influenza Vaccine Recommendations

- All persons 50 years of age or older
- Healthy children 6 months through 18 years of age
- Residents of long-term care facilities
- Pregnant women
- Persons 6 months through 18 years receiving chronic aspirin therapy
- Persons 6 months of age and older with chronic illness

Inactivated Influenza Vaccine Recommendations

- Persons with the following chronic illnesses should be considered for inactivated influenza vaccine:
  - pulmonary (e.g., asthma, COPD)
  - cardiovascular (e.g., CHF)
  - metabolic (e.g., diabetes)
  - renal dysfunction
  - hemoglobinopathy
  - immunosuppression, including HIV infection
  - any condition that can compromise respiratory function or the handling of respiratory secretions

Inactivated influenza vaccine should be given by the intramuscular (IM) route. Other methods, such as intradermal, subcutaneous, topical, or mucosal should not be used unless approved by the Food and Drug Administration or recommended by ACIP.

TIV is recommended for all persons 50 years of age or older and all children 6 months through 18 years of age, regardless of the presence of chronic illness. Other groups targeted for TIV include residents of long-term care facilities, pregnant women, and persons 6 months through 18 years of age receiving chronic aspirin therapy (because of the risk of Reye syndrome following influenza infection).

Persons 6 months of age and older with a chronic illness should receive TIV annually. These chronic illnesses include the following:

- pulmonary illnesses, such as emphysema, chronic bronchitis, or asthma
- cardiovascular illnesses, such as congestive heart failure

- metabolic diseases, including diabetes mellitus
- renal dysfunction
- hemoglobinopathy, such as sickle cell disease
- immunosuppression, including human immunodeficiency virus (HIV) infection
- any condition (e.g., cognitive dysfunction, spinal cord injury, seizure disorder, or other neuromuscular disorder) that can compromise respiratory function or the handling of respiratory secretions

Case reports and limited studies suggest that pregnant women may be at increased risk for serious medical complications of influenza as a result of increases in heart rate, stroke volume and oxygen consumption; decreases in lung capacity; and changes in immunologic function. A study found that the risk of hospitalization for influenza-related complications was more than four times higher for women in the second or third trimester of pregnancy than for nonpregnant women. The risk of complications for these pregnant women was comparable to that for nonpregnant women with high-risk medical conditions, for whom influenza vaccine has been traditionally recommended.

Pregnancy and Inactivated Influenza Vaccine

- Risk of hospitalization 4 times higher than nonpregnant women
- Risk of complications comparable to nonpregnant women with high-risk medical conditions
- Vaccination (with TIV) recommended if pregnant during influenza season
- Vaccination can occur during any trimester

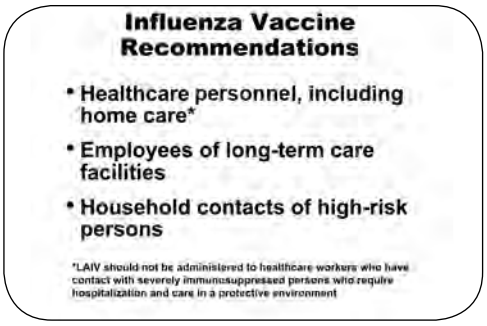
ACIP recommends vaccination of women who will be pregnant during influenza season. Vaccination can occur during any trimester. Influenza season in the United States generally occurs in December through March. Only TIV should be administered to pregnant women.

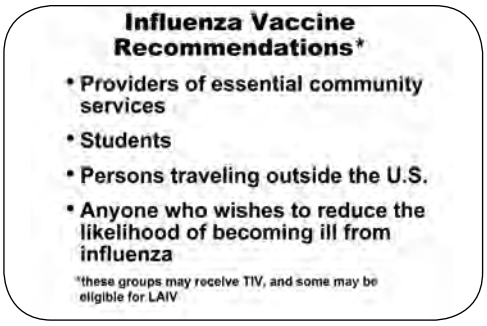
Available data suggest that persons with HIV infection may have prolonged influenza illnesses and are at increased risk of complications of influenza. Many persons with HIV infection will develop protective antibody titers following inactivated influenza vaccine. In persons who have advanced HIV disease and low CD4+ T-lymphocyte cell counts, TIV vaccine may not induce protective antibody titers. A second dose of vaccine does not improve the immune response in these persons.

HIV Infection and Inactivated Influenza Vaccine

- Persons with HIV at increased risk of complications of influenza
- TIV induces protective antibody titers in many HIV-infected persons
- Transient increase in HIV replication reported
- TIV will benefit many HIV-infected persons

Some studies have demonstrated a transient increase in viral titer in the blood of vaccinated persons infected with HIV. There is no evidence of deterioration in CD4 counts or progression of clinical HIV disease. Because influenza can result in serious illness and complications and because influenza vaccination may result in protective antibody titers, ACIP believes that influenza vaccination will benefit many persons with HIV infection. LAIV should not be administered to persons with HIV infection.





Persons who have contact with high-risk persons should receive TIV. These include healthcare personnel, employees of long-term care facilities, and household contacts of high-risk persons. These individuals may be younger and healthier and more likely to be protected from illness than are elderly persons. All healthcare providers should receive annual inactivated influenza vaccine. Groups that should be targeted include physicians, nurses, and other personnel in hospitals and outpatient settings who have contact with high-risk patients in all age groups, and providers of home care to high-risk persons (e.g., visiting nurses, volunteers). LAIV may be administered to healthy healthcare personnel 49 years of age or younger, except those who have contact with severely immunosuppressed persons who require hospitalization and care in a protective environment (i.e., in isolation because of severe immunosuppression).

Persons who provide essential community services and students or others in institutional settings (e.g., schools and colleges) may be considered for vaccination to minimize disruption of routine activities during outbreaks. Persons traveling outside the United States should consider influenza vaccination. The risk of exposure to influenza during foreign travel varies, depending on season of travel, the mode of travel (e.g., increased risk during cruises), and destination. Influenza can occur throughout the year in the tropics. In the Southern Hemisphere, influenza activity peaks in April–September. If not vaccinated the previous fall/winter, persons (especially those in high-risk groups) preparing to travel to the tropics at any time of the year or to the Southern Hemisphere during April–September should be considered for influenza vaccination before travel. Any person who wishes to lessen his/her chance of acquiring influenza infection may be vaccinated.

In 2005, the ACIP recommended routine vaccination of all children 6 through 59 months of age because of the increased risk of influenza-related hospitalization and physician visits in this age group. Household contacts and other caregivers of children younger than 59 months of age are also encouraged to receive annual influenza vaccination.

LAIV

LAIV is approved for healthy, nonpregnant persons 2 through 49 years of age. The vaccine can be administered to eligible persons as soon as it becomes available in the late summer or fall. Vaccination can continue throughout influenza season. One dose of LAIV may be administered by the intranasal route to persons 9 through 49 years of age. Children 2 through 8 years of age receiving influenza

vaccine for the first time should receive two doses administered at least 4 weeks apart.

Live Attenuated Influenza Vaccine Dosage, by Age Group – United States

Age Group	Number of Doses	Route
2-8 years, no previous influenza vaccine	2 (separated by 4 weeks)	Intranasal
5-8 years, previous influenza vaccine*	1† or 2	Intranasal
9-49 years	1	Intranasal

*LAIV or inactivated vaccine

†Only one dose is needed if the child received two doses of influenza vaccine during a previous influenza season.

Close contacts of persons at high risk for complications from influenza should receive influenza vaccine. This reduces the risk of transmission of wild-type influenza viruses to high-risk persons. Contacts of persons at high risk of complications of influenza may receive LAIV if they are otherwise eligible (i.e., 2 through 49 years of age, healthy and not pregnant). Persons in close contact with severely immunosuppressed persons who are hospitalized and receiving care in a protected environment should not receive LAIV.

Inactivated vaccines do not interfere with the immune response to live vaccines. Inactivated vaccines, such as tetanus and diphtheria toxoids, can be administered either simultaneously or at any time before or after LAIV. Other live vaccines can be administered on the same day as LAIV. Live vaccines not administered on the same day should be administered at least 4 weeks apart when possible.

Simultaneous Administration of LAIV and Other Vaccines

- Inactivated vaccines can be administered either simultaneously or at any time before or after LAIV
- Other live vaccines can be administered on the same day as LAIV
- Live vaccines not administered on the same day should be administered ≥4 weeks apart

Contraindications and Precautions to Vaccination

TIV

Persons with a severe allergic reaction (anaphylaxis) to a vaccine component or following a prior dose of inactivated influenza vaccine should not receive TIV. Persons with a moderate or severe acute illness normally should not be vaccinated until their symptoms have decreased. Pregnancy, breastfeeding, and immunosuppression are not contraindications to inactivated influenza vaccination.

Inactivated Influenza Vaccine Contraindications and Precautions

- Severe allergic reaction to a vaccine component (e.g., egg) or following a prior dose of vaccine
- Moderate or severe acute illness

LAIV

Persons who should not receive LAIV include children younger than 2 years of age; persons 50 years of age and older; persons with chronic medical conditions, including asthma, a recent wheezing episode, reactive airways disease or other chronic pulmonary or cardiovascular conditions,

Live Attenuated Influenza Vaccine Contraindications and Precautions

- Children <2 years of age*
- Persons ≥50 years of age*
- Persons with chronic medical conditions*
- Children and adolescents receiving long-term aspirin therapy*

*These persons should receive inactivated influenza vaccine

metabolic disease such as diabetes, renal disease, or hemoglobinopathy, such as sickle cell disease; and children or adolescents receiving long-term therapy with aspirin or other salicylates, because of the association of Reye syndrome with wild-type influenza infection. Persons in these groups should receive inactivated influenza vaccine.

Live Attenuated Influenza Vaccine Contraindications and Precautions

- Immunosuppression from any cause
- Pregnant women*
- Severe (anaphylactic) allergy to egg or other vaccine components
- History of Guillian-Barré syndrome
- Moderate or severe acute illness

*These persons should receive inactivated influenza vaccine

As with other live-virus vaccines, LAIV should not be given to persons who are immunosuppressed because of disease, including HIV, or who are receiving immunosuppressive therapy. Pregnant women should not receive LAIV. Immunosuppressed persons and pregnant women should receive inactivated influenza vaccine. Since LAIV contains residual egg protein, it should not be administered to persons with a history of severe allergy to egg or any other vaccine component. The manufacturer recommends that LAIV not be administered to a person with a history of Guillain-Barré syndrome.

As with all vaccines, LAIV should be deferred for persons with a moderate or severe acute illness. If clinical judgment indicates that nasal congestion might impede delivery of the vaccine to the nasopharyngeal mucosa, deferral of administration should be considered until the condition has improved.

The effect on safety and efficacy of LAIV coadministration with influenza antiviral medications has not been studied. However, because influenza antiviral agents reduce replication of influenza viruses, LAIV should not be administered until 48 hours after cessation of influenza antiviral therapy, and influenza antiviral medications should not be administered for 2 weeks after receipt of LAIV.

Adverse Reactions Following Vaccination

TIV

Inactivated Influenza Vaccine Adverse Reactions

Local reactions	15%-20%
Fever, malaise	not common
Allergic reactions	rare
Neurological reactions	very rare

Local reactions are the most common adverse reactions following vaccination with TIV. Local reactions include soreness, erythema, and induration at the site of injection. These reactions are transient, generally lasting 1 to 2 days. Local reactions are reported in 15%–20% of vaccinees.

Nonspecific systemic symptoms, including fever, chills, malaise, and myalgia, are reported in fewer than 1% of TIV recipients. These symptoms usually occur in those with no previous exposure to the viral antigens in the vaccine. They usually occur within 6–12 hours of TIV vaccination and last 1–2 days. Recent reports indicate that these systemic symptoms are no more common than in persons given a placebo injection.

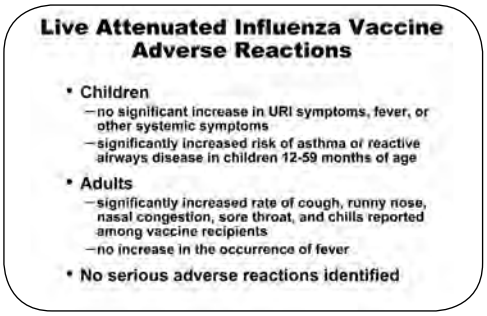
Rarely, immediate hypersensitivity, presumably allergic, reactions (such as hives, angioedema, allergic asthma, or

systemic anaphylaxis) occur after vaccination with TIV. These reactions probably result from hypersensitivity to a vaccine component. The majority are most likely related to residual egg protein. Although current influenza vaccines contain only a small quantity of egg protein, this protein may induce immediate allergic reactions in persons with severe egg allergy. Persons who have developed hives, had swelling of the lips or tongue, or have experienced acute respiratory distress or collapse after eating eggs should consult a physician for appropriate evaluation to assist in determining whether influenza vaccination may proceed or should be deferred. Persons with documented immunoglobulin E (IgE)-mediated hypersensitivity to eggs—including those who have had occupational asthma or other allergic responses from exposure to egg protein—may also be at increased risk for reactions from influenza vaccines, and similar consultation should be considered. Protocols have been published for influenza vaccination of patients who have egg allergies and medical conditions that place them at increased risk for influenza infection or its complications.

The potential exists for hypersensitivity reactions to any vaccine component. Although exposure to vaccines containing thimerosal can lead to induction of hypersensitivity, most patients do not develop reactions to thimerosal administered as a component of vaccines, even when patch or intradermal tests for thimerosal indicate hypersensitivity. When it has been reported, hypersensitivity to thimerosal has usually consisted of local delayed-type hypersensitivity reactions.

Unlike the 1976 swine influenza vaccine, subsequent inactivated vaccines prepared from other virus strains have not been clearly associated with an increased frequency of Guillain-Barré syndrome (GBS). However, obtaining a precise estimate of a small increase in risk is difficult for a rare condition such as GBS, which has an annual background incidence of only one to two cases per 100,000 adult population. Among persons who received the swine influenza vaccine in 1976, the rate of GBS exceeded the background rate by less than one case per 100,000 vaccinations. Even if GBS were a true adverse reaction in subsequent years, the estimated risk for GBS was much lower than one per 100,000. Further, the risk is substantially less than that for severe influenza or its complications, which could be prevented by vaccination, especially for persons aged 65 years or older and those with a medical indication for influenza vaccine.

Although the incidence of GBS in the general population is very low, persons with a history of GBS have a substantially greater likelihood of subsequently developing GBS than do persons without such a history, irrespective of vaccination. As a result, the likelihood of coincidentally developing GBS



after influenza vaccination is expected to be greater among persons with a history of GBS than among persons with no history of GBS. Whether influenza vaccination might be causally associated with this risk for recurrence is not known. It seems prudent for persons known to have developed GBS within 6 weeks of a previous influenza vaccination to avoid subsequent influenza vaccination. For most persons with a history of GBS who are at high risk for severe complications from influenza, the established benefits of influenza vaccination justify yearly vaccination.

LAIV

Among children the most common adverse reactions are runny nose and headaches. However, there have been no significant differences between LAIV and placebo recipients in the proportion with these symptoms. In a clinical trial, children 6–23 months of age had an increased risk of wheezing. An increased risk of wheezing was not reported in older children.

Among healthy adults, a significantly increased rate of cough, runny nose, nasal congestion, sore throat, and chills was reported among vaccine recipients. These symptoms were reported in 10%–40% of vaccine recipients, a rate 3%–10% higher than reported for placebo recipients. There was no increase in the occurrence of fever among vaccine recipients. No serious adverse reactions have been identified in LAIV recipients, either children or adults.

No instances of Guillain-Barré syndrome have been reported among LAIV recipients. However the number of persons vaccinated to date is too small to identify such a rare vaccine adverse reaction.

Few data are available concerning the safety of LAIV among persons at high risk for development of complications of influenza, such as immunosuppressed persons or those with chronic pulmonary or cardiac disease. Until additional data are available, persons at high risk of complications of influenza should not receive LAIV. These persons should continue to receive inactivated influenza vaccine.

Vaccine Storage and Handling

TIV

Inactivated influenza vaccine is generally shipped in an insulated container with coolant packs. Although some brands of TIV vaccine can tolerate room temperature for a few days, CDC recommends that the vaccine be stored at refrigerator temperature (35°–46°F [2°–8°C]). Inactivated influenza vaccine must not be frozen. Opened multidose vials may be used until the expiration date printed on the package if no visible contamination is present.

LAIV

LAIV should be stored at refridgerator temperature (35°– 46° F [2°–8°C]). LAIV inadvertently exposed to freezing temperature should be placed at refrigerator temperature and used as soon as possible.

LAIV is intended for intranasal administration only and should never be administered by injection. LAIV is supplied in a prefilled single-use sprayer containing 0.2 mL of vaccine. Approximately 0.1 mL (i.e., half of the total sprayer contents) is sprayed into the first nostril while the recipient is in the upright position. An attached dose-divider clip is removed from the sprayer to administer the second half of the dose into the other nostril. If the vaccine recipient sneezes after administration, the dose should not be repeated.

Year 2010 Objectives and Coverage Levels

Year 2010 objectives are to increase influenza vaccination levels to 60% or higher among high-risk populations (90% in residents of long-term care facilities) and to reduce epidemic-related pneumonia and influenza-related deaths among persons 65 years of age and older. In 2006–2007, 66% of persons 65 years of age and older reported receiving influenza vaccine in the previous year. Vaccination levels were lower among black and Hispanic persons than among non-Hispanic white persons.

Strategies for Improving Influenza Vaccine Coverage

On average, fewer than 20% of persons in high-risk groups receive influenza vaccine each year. This points to the need for more effective strategies for delivering vaccine to high-risk persons, their healthcare providers, and household contacts. Persons for whom the vaccine is recommended can be identified and immunized in a variety of settings.

Influenza Vaccine Strategies to Improve Coverage

- Ensure systematic and automatic offering of TIV to high-risk groups
- Educate healthcare providers and patients
- Address concerns about adverse events
- Emphasize physician recommendation

In physicians' offices and outpatient clinics, persons who should receive inactivated influenza vaccine should be identified and their charts marked. TIV use should be promoted, encouraged and recommended beginning in October and continuing through the influenza season. Those without regularly scheduled visits should receive reminders.

In nursing homes and other residential long-term care facilities, immunization with TIV should be routinely provided to all residents at one period of time immediately preceding the influenza season; consent should be obtained at the time of admission.

In acute care hospitals and continuing care centers, persons

for whom vaccine is recommended who are hospitalized from October through March should be vaccinated prior to discharge. In outpatient facilities providing continuing care to high-risk patients (e.g., hemodialysis centers, hospital specialty-care clinics, outpatient rehabilitation programs), all patients should be offered TIV shortly before the onset of the influenza season.

Visiting nurses and others providing home care to high-risk persons should identify high-risk patients and administer TIV in the home, if necessary.

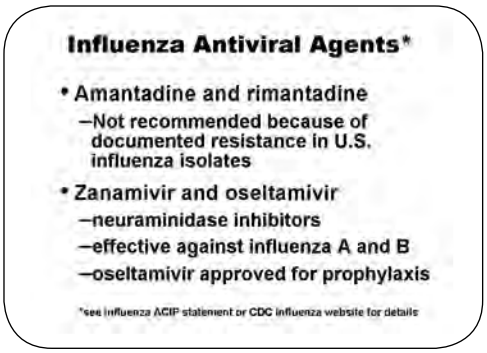
In facilities providing services to persons 50 years of age and older (e.g., retirement communities, recreation centers), inactivated influenza vaccine should be offered to all unvaccinated residents or attendees on site. Education and publicity programs should also be conducted in conjunction with other interventions.

For travelers, indications for influenza vaccine should be reviewed prior to travel and vaccine offered, if appropriate.

Administrators of all of the above facilities and organizations should arrange for influenza vaccine to be offered to all personnel before the influenza season. Additionally, household members of high-risk persons and others with whom they will be in contact should receive written information about why they should receive the vaccine and where to obtain it.

Antiviral Agents for Influenza

In the United States, four antiviral agents are approved for preventing or treating influenza: amantadine, rimantadine, zanamivir, and oseltamivir.



Testing of influenza A isolates from the United States and Canada has demonstrated that many of these viruses are resistant to amantadine and rimantadine. The ACIP recommends that neither amantadine nor rimantadine be used for the treatment or chemoprophylaxis of influenza A in the United States until susceptibility to these antiviral drugs has been re-established.

Zanamivir and oseltamivir are members of a new class of drugs called neuraminidase inhibitors and are active against both influenza type A and type B. Zanamivir is provided as a dry powder that is administered by inhalation. It is approved for treatment of uncomplicated acute influenza A or B in persons 7 years of age and older who have been symptomatic for no more than 48 hours. Oseltamivir is provided as an oral capsule. It is approved for the treatment of uncomplicated influenza A or B in persons 1 year of age and older who have been symptomatic for no more than 48 hours. Zanamivir is approved for prophylaxis of influenza

in persons 5 years and older. Oseltamivir is approved for prophylaxis of influenza infection among persons 1 year of age and older.

In 2007-08, a significant increase in the prevalence of oseltamivir resistance was reported among influenza A (H1N1) viruses worldwide. During the 2007-08 influenza season, 10.9% of H1N1 viruses tested in the U.S. were resistant to oseltamivir. During 2008 more than 90% of H1N1 viruses were resistant to oseltamivir. For the 2008-09 influenza season CDC recommends that persons who test positive for influenza A should receive only zanamivir if treatment is indicated. Oseltamivir should be used alone only if recent local surveillance data indicate that circulating viruses are likely to be influenza A (H3N2) or influenza B viruses, which have not been found to be resistant to oseltamivir. Additional information about influenza antiviral treatment is available on the CDC influenza website.

Antiviral agents for influenza are an adjunct to vaccine and are not a substitute for vaccine. Vaccination remains the principal means for preventing influenza-related morbidity and mortality. Additional information on the use of influenza antiviral drugs can be found in the current ACIP statement on influenza vaccine and on the CDC influenza website at http://www.cdc.gov/flu.

Nosocomial Influenza Control

Many patients in general hospitals, and especially in referral centers, are likely to be at high risk for complications of influenza. Hospitalized susceptible patients may acquire influenza from patients, hospital employees, or visitors. The preferred method of control is to administer inactivated influenza vaccine to high-risk patients and medical personnel prior to the outbreak.

During community influenza A activity, the use of antiviral prophylaxis may be considered for high-risk patients who were not immunized or were immunized too recently to have protective antibody levels. Antiviral agents may also be considered for unimmunized hospital personnel. Other measures include restricting visitors with respiratory illness, cohorting patients with influenza for 5 days following onset of illness, and postponing elective admission of patients with uncomplicated illness.

Influenza Surveillance

Influenza surveillance is intended to monitor the prevalence of circulating strains and detect new strains necessary for vaccine formulation; estimate influenza-related impact on morbidity, mortality, and economic loss; rapidly detect outbreaks; and assist disease control through rapid preven-

Influenza Surveillance

- Monitor prevalence of circulating strains and detect new strains
- Estimate influenza-related morbidity, mortality and economic loss
- Rapidly detect outbreaks
- Assist disease control through rapid preventive action

tive action (e.g., chemoprophylaxis of unvaccinated high-risk patients).

CDC receives weekly surveillance reports from the states showing the extent of influenza activity. Reports are classified into four categories: no cases, sporadic, regional (cases occurring in counties collectively contributing less than 50% of a state's population), widespread (cases occurring in counties collectively contributing 50% or more of a state's population).

Weekly surveillance reports are available at http://www.cdc.gov/flu/weekly/fluactivity.htm

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Influenza

10

Measles

Measles is an acute viral infectious disease. References to measles can be found from as early as the 7th century. The disease was described by the Persian physician Rhazes in the 10th century as "more dreaded than smallpox."

In 1846, Peter Panum described the incubation period of measles and lifelong immunity after recovery from the disease. Enders and Peebles isolated the virus in human and monkey kidney tissue culture in 1954. The first live attenuated vaccine was licensed for use in the United States in 1963 (Edmonston B strain).

Before a vaccine was available, infection with measles virus was nearly universal during childhood, and more than 90% of persons were immune by age 15 years. Measles is still a common and often fatal disease in developing countries. The World Health Organization estimates there were more than 20 million cases and 242,000 deaths from measles in 2006.

Measles

- Highly contagious viral illness
- First described in 7th century
- Near universal infection of childhood in prevaccination era
- Common and often fatal in developing countries

Measles Virus

The measles virus is a paramyxovirus, genus *Morbillivirus*. It is 100–200 nm in diameter, with a core of single-stranded RNA, and is closely related to the rinderpest and canine distemper viruses. Two membrane envelope proteins are important in pathogenesis. They are the F (fusion) protein, which is responsible for fusion of virus and host cell membranes, viral penetration, and hemolysis, and the H (hemagglutinin) protein, which is responsible for adsorption of virus to cells.

There is only one antigenic type of measles virus. Although studies have documented changes in the H glycoprotein, these changes do not appear to be epidemiologically important (i.e., no change in vaccine efficacy has been observed).

Measles virus is rapidly inactivated by heat, light, acidic pH, ether, and trypsin. It has a short survival time (less than 2 hours) in the air or on objects and surfaces.

Measles Virus

- Paramyxovirus (RNA)
- Hemagglutinin important surface antigen
- One antigenic type
- Rapidly inactivated by heat and light

Pathogenesis

Measles is a systemic infection. The primary site of infection is the respiratory epithelium of the nasopharynx. Two to three days after invasion and replication in the respiratory epithelium and regional lymph nodes, a primary viremia occurs with subsequent infection of the reticuloendothelial system. Following further viral replication in regional and distal reticuloendothelial sites, a second viremia occurs 5–7 days after initial infection. During this viremia, there may be infection of the respiratory tract and other organs. Measles virus is shed from the nasopharynx beginning with the prodrome until 3–4 days after rash onset.

Measles Pathogenesis

- Respiratory transmission of virus
- Replication in nasopharynx and regional lymph nodes
- Primary viremia 2-3 days after exposure
- Secondary viremia 5-7 days after exposure with spread to tissues

Measles

Measles Clinical Features

- Incubation period 10-12 days

Prodrome

- Stepwise increase in fever to 103°F or higher
- Cough, coryza, conjunctivitis
- Koplik spots

Measles Clinical Features

Rash

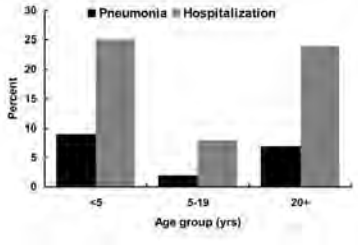
- 2-4 days after prodrome, 14 days after exposure
- Persists 5-6 days
- Begins on face and head
- Maculopapular, becomes confluent
- Fades in order of appearance

Measles Complications

Condition	Percent reported
Diarrhea	8
Otitis media	7
Pneumonia	6
Encephalitis	0.1
Seizures	0.6 – 0.7
Death	0.2

Based on 1985-1992 surveillance data

Measles Complications by Age Group



Clinical Features

The incubation period of measles, from exposure to prodrome averages 10–12 days. From exposure to rash onset averages 14 days (range, 7–18 days).

The prodrome lasts 2–4 days (range 1–7 days). It is characterized by fever, which increases in stepwise fashion, often peaking as high as 103°–105°F. This is followed by the onset of cough, coryza (runny nose), or conjunctivitis.

Koplik spots, a rash (enanthem) present on mucous membranes, is considered to be pathognomonic for measles. It occurs 1–2 days before the rash to 1–2 days after the rash, and appears as punctate blue-white spots on the bright red background of the buccal mucosa.

The measles rash is a maculopapular eruption that usually lasts 5–6 days. It begins at the hairline, then involves the face and upper neck. During the next 3 days, the rash gradually proceeds downward and outward, reaching the hands and feet. The maculopapular lesions are generally discrete, but may become confluent, particularly on the upper body. Initially, lesions blanch with fingertip pressure. By 3–4 days, most do not blanch with pressure. Fine desquamation occurs over more severely involved areas. The rash fades in the same order that it appears, from head to extremities.

Other symptoms of measles include anorexia, diarrhea, especially in infants, and generalized lymphadenopathy.

Complications

Approximately 30% of reported measles cases have one or more complications. Complications of measles are more common among children younger than 5 years of age and adults 20 years of age and older.

From 1985 through 1992, diarrhea was reported in 8% of measles cases, making this the most commonly reported complication of measles. Otitis media was reported in 7% of cases and occurs almost exclusively in children. Pneumonia (in 6% of reported cases) may be viral or superimposed bacterial, and is the most common cause of death.

Acute encephalitis occurs in approximately 0.1% of reported cases. Onset generally occurs 6 days after rash onset (range 1–15 days) and is characterized by fever, headache, vomiting, stiff neck, meningeal irritation, drowsiness, convulsions, and coma. Cerebrospinal fluid shows pleocytosis and elevated protein. The case-fatality rate is approximately 15%. Some form of residual neurologic damage occurs in as many as 25% of cases. Seizures (with or without fever) are reported in 0.6%–0.7% of cases.

Death from measles was reported in approximately 0.2% of the cases in the United States from 1985 through 1992. As with other complications of measles, the risk of death is higher among young children and adults. Pneumonia accounts for about 60% of deaths. The most common causes of death are pneumonia in children and acute encephalitis in adults. Since 1995, an average of 1 measles-related death per year has been reported.

Subacute sclerosing panencephalitis (SSPE) is a rare degenerative central nervous system disease believed to be due to persistent measles virus infection of the brain. Onset occurs an average of 7 years after measles (range 1 month–27 years), and occurs in five to ten cases per million reported measles cases. The onset is insidious, with progressive deterioration of behavior and intellect, followed by ataxia (awkwardness), myoclonic seizures, and eventually death. SSPE has been extremely rare since the early 1980s.

Measles illness during pregnancy results in a higher risk of premature labor, spontaneous abortion, and low-birthweight infants. Birth defects (with no definable pattern of malformation) have been reported rarely, without confirmation that measles was the cause.

Atypical measles occurs only in persons who received inactivated ("killed") measles vaccine (KMV) and are subsequently exposed to wild-type measles virus. An estimated 600,000 to 900,000 persons received KMV in the United States from 1963 to 1967. KMV sensitizes the recipient to measles virus antigens without providing protection. Subsequent infection with measles virus leads to signs of hypersensitivity polyserositis. The illness is characterized by fever, pneumonia, pleural effusions, and edema. The rash is usually maculopapular or petechial, but may have urticarial, purpuric, or vesicular components. It appears first on the wrists or ankles. Atypical measles may be prevented by revaccinating with live measles vaccine. Moderate to severe local reactions with or without fever may follow vaccination; these reactions are less severe than with infection with wild measles virus.

Modified measles occurs primarily in patients who received immune globulin (IG) as postexposure prophylaxis and in young infants who have some residual maternal antibody. It is usually characterized by a prolonged incubation period, mild prodrome, and sparse, discrete rash of short duration. Similar mild illness has been reported among previously vaccinated persons.

Rarely reported in the United States, hemorrhagic measles is characterized by high fever (105°–106°F), seizures, delirium, respiratory distress, and hemorrhage into the skin and mucous membranes.

Measles in an immunocompromised person may be severe with a prolonged course. It is reported almost exclusively in persons with T-cell deficiencies (certain leukemias, lymphomas, and acquired immunodeficiency syndrome [AIDS]). It may occur without the typical rash, and a patient may shed virus for several weeks after the acute illness.

Measles in developing countries has resulted in high attack rates among children younger than 12 months of age. Measles is more severe in malnourished children, particularly those with vitamin A deficiency. Complications include diarrhea, dehydration, stomatitis, inability to feed, and bacterial infections (skin and elsewhere). The case-fatality rate may be as high as 25%. Measles is also a leading cause of blindness in African children.

Laboratory Diagnosis

Measles Laboratory Diagnosis

- Isolation of measles virus from a clinical specimen (e.g., urine, nasopharynx)
- Significant rise in measles IgG by any standard serologic assay (e.g., EIA, HA)
- Positive serologic test for measles IgM antibody

Isolation of measles virus is not recommended as a routine method to diagnose measles. However, virus isolates are extremely important for molecular epidemiologic surveillance to help determine the geographic origin of the virus and the viral strains circulating in the United States.

Measles virus can be isolated from urine, nasopharyngeal aspirates, heparinized blood, or throat swabs. Specimens for virus culture should be obtained from every person with a clinically suspected case of measles and should be shipped to the state public health laboratory or CDC, at the direction of the state health department. Clinical specimens for viral isolation should be collected at the same time as samples taken for serologic testing. Because the virus is more likely to be isolated when the specimens are collected within 3 days of rash onset, collection of specimens for virus isolation should not be delayed until serologic confirmation is obtained. Clinical specimens should be obtained within 7 days, and not more than 10 days, after rash onset. A detailed protocol for collection of specimens for viral isolation is available on the CDC website at http://www.cdc.gov/ncidod/dvrd/revb/measles/viral_isolation.htm.

Serologic testing, most commonly by enzyme-linked immunoassay (ELISA or EIA), is widely available and may be diagnostic if done at the appropriate time. Generally, a previously susceptible person exposed to either vaccine or wild-type measles virus will first mount an IgM response and then an IgG response. The IgM response will be transient (1–2 months), and the IgG response should persist for many years. Uninfected persons should be IgM negative and will be either IgG negative or IgG positive, depending upon their previous infection history.

ELISA for IgM antibody requires only a single serum specimen and is diagnostic if positive. The preferred reference test is a

capture IgM test developed by CDC. This test should be used to confirm every case of measles that is reported to have some other type of laboratory confirmation. IgM capture tests for measles are often positive on the day of rash onset. However, in the first 72 hours after rash onset, up to 20% of tests for IgM may give false-negative results. Tests that are negative in the first 72 hours after rash onset should be repeated. IgM is detectable for at least 28 days after rash onset and frequently longer.

A variety of tests for IgG antibodies to measles are available and include ELISA, hemagglutination inhibition (HI), indirect fluorescent antibody tests, microneutralization, and plaque reduction neutralization. Complement fixation, while widely used in the past, is no longer recommended.

IgG testing for acute measles requires demonstration of a rise in titer of antibody against measles virus, so two serum specimens are always required. The first specimen should be drawn as soon after rash onset as possible. The second specimen should be drawn 10–30 days later. The tests for IgG antibody should be conducted on both specimens at the same time. The same type of test should be used on both specimens. The specific criteria for documenting an increase in titer depend on the test.

Tests for IgG antibody require two serum specimens, and a confirmed diagnosis cannot be made until the second specimen is obtained. As a result, IgM tests are generally preferred to confirm the diagnosis of measles.

Epidemiology

Occurrence

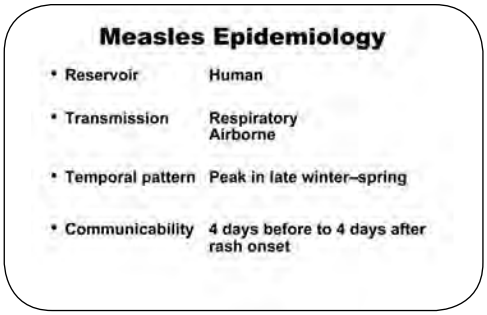
Measles occurs throughout the world. However, interruption of indigenous transmission of measles has been achieved in the United States and other parts of the Western Hemisphere.

Reservoir

Measles is a human disease. There is no known animal reservoir, and an asymptomatic carrier state has not been documented.

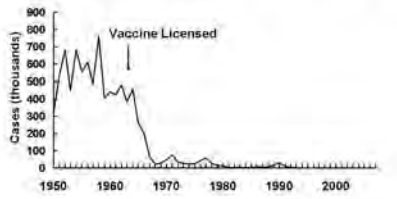
Transmission

Measles transmission is primarily person to person via large respiratory droplets. Airborne transmission via aerosolized droplet nuclei has been documented in closed areas (e.g., office examination room) for up to 2 hours after a person with measles occupied the area.

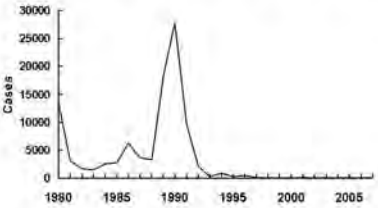


Measles

Measles - United States, 1950-2007



Measles - United States, 1980-2007



Measles Resurgence—United States, 1989-1991

• Cases	55,622
• Age group affected	Children <5 yrs
• Deaths	123

Temporal Pattern

In temperate areas, measles disease occurs primarily in late winter and spring.

Communicability

Measles is highly communicable, with greater than 90% secondary attack rates among susceptible persons. Measles may be transmitted from 4 days before to 4 days after rash onset. Maximum communicability occurs from onset of prodrome through the first 3–4 days of rash.

Secular Trends in the United States

Before 1963, approximately 500,000 cases and 500 deaths were reported annually, with epidemic cycles every 2–3 years. However, the actual number of cases was estimated at 3–4 million annually. More than 50% of persons had measles by age 6, and more than 90% had measles by age 15. The highest incidence was among 5–9-year-olds, who generally accounted for more than 50% of reported cases.

Following licensure of vaccine in 1963, the incidence of measles decreased by more than 98%, and 2–3-year epidemic cycles no longer occurred. Because of this success, a 1978 Measles Elimination Program set a goal to eliminate indigenous measles by October 1, 1982 (26,871 cases were reported in 1978). The 1982 elimination goal was not met, but in 1983, only 1,497 cases were reported (0.6 cases per 100,000 population), the lowest annual total ever reported up to that time.

During 1980–1988, a median of 57% of reported cases were among school-aged persons (5–19 years of age), and a median of 29% were among children younger than 5 years of age. A median of 8% of cases were among infants younger than 1 year of age.

From 1985 through 1988, 42% of cases occurred in persons who were vaccinated on or after their first birthday. During these years, 68% of cases in school-aged children (5–19 years) occurred among those who had been appropriately vaccinated. The occurrence of measles among previously vaccinated children (i.e., vaccine failure) led to the recommendation for a second dose in this age group.

Measles Resurgence in 1989–1991

From 1989 through 1991, a dramatic increase in cases occurred. During these 3 years a total of 55,622 cases were reported (18,193 in 1989; 27,786 in 1990; 9,643 in 1991). In addition to the increased number of cases, a change occurred in their age distribution. Prior to the resurgence, school-aged children had accounted for the largest proportion of

reported cases. During the resurgence, 45% of all reported cases were in children younger than 5 years of age. In 1990, 48% of patients were in this age group, the first time that the proportion of cases in children younger than 5 years of age exceeded the proportion of cases in 5–19-year-olds (35%).

Overall incidence rates were highest for Hispanics and blacks and lowest for non-Hispanic whites. Among children younger than 5 years of age, the incidence of measles among blacks and Hispanics was four to seven times higher than among non-Hispanic whites.

A total of 123 measles-associated deaths were reported (death-to-case ratio of 2.2 per 1,000 cases). Forty-nine percent of deaths were among children younger than 5 years of age. Ninety percent of fatal cases occurred among persons with no history of vaccination. Sixty-four deaths were reported in 1990, the largest annual number of deaths from measles since 1971.

The most important cause of the measles resurgence of 1989–1991 was low vaccination coverage. Measles vaccine coverage was low in many cities, including some that experienced large outbreaks among preschool-aged children throughout the early to mid-1980s. Surveys in areas experiencing outbreaks among preschool-aged children indicated that as few as 50% of children had been vaccinated against measles by their second birthday, and that black and Hispanic children were less likely to be age-appropriately vaccinated than were white children.

In addition, measles susceptibility of infants younger than 1 year of age may have increased. During the 1989–1991 measles resurgence, incidence rates for infants were more than twice as high as those in any other age group. The mothers of many infants who developed measles were young, and their measles immunity was most often due to vaccination rather than infection with wild virus. As a result, a smaller amount of antibody was transferred across the placenta to the fetus, compared with antibody transfer from mothers who had higher antibody titers resulting from wild-virus infection. The lower quantity of antibody resulted in immunity that waned more rapidly, making infants susceptible at a younger age than in the past.

The increase in measles in 1989–1991 was not limited to the United States. Large outbreaks of measles were reported by many other countries of North and Central America, including Canada, El Salvador, Guatemala, Honduras, Jamaica, Mexico, and Nicaragua.

Measles

Measles 1993-2007

- Endemic transmission interrupted
- Record low annual total in 2004 (37 total cases)
- Many cases among adults
- Most cases imported or linked to importation

Measles Since 1993

Reported cases of measles declined rapidly after the 1989–1991 resurgence. This decline was due primarily to intensive efforts to vaccinate preschool-aged children. Measles vaccination levels among 2-year-old children increased from 70% in 1990 to 91% in 1997.

Since 1993, fewer than 500 cases have been reported annually, and fewer than 200 cases per year have been reported since 1997. A record low annual total of 37 cases was reported in 2004. Available epidemiologic and virologic data indicate that measles transmission in the United States has been interrupted. The majority of cases are now imported from other countries or linked to imported cases. Most imported cases originate in Asia and Europe and occur both among U.S. citizens traveling abroad and persons visiting the United States from other countries. An aggressive measles vaccination program by the Pan American Health Organization has resulted in record low measles incidence in Latin America and the Caribbean, and the interruption of indigenous measles transmission in the Americas. Measles elimination from the Americas was achieved in 2002 and has been sustained since then, with only imported and importation-related measles cases occuring in the region.

Since the mid-1990s, no age group has predominated among reported cases of measles. Relative to earlier decades, an increased proportion of cases now occur among adults. In 1973, persons 20 years of age and older accounted for only about 3% of cases. In 1994, adults accounted for 24% of cases, and in 2001, for 48% of all reported cases.

The size and makeup of measles outbreaks has changed since the 1980s. Prior to 1989, the majority of outbreaks occurred among middle, high school and college student populations. As many as 95% of persons infected during these outbreaks had received one prior dose of measles vaccine. A second dose of measles vaccine was recommended for school-aged children in 1989, and all states now require two doses of measles vaccine for school-aged children. As a result, measles outbreaks in school settings are now uncommon.

In 2008 a provisional total of 132 measles cases was reported, the largest annual total since 1997. Eighty nine percent of these cases were imported from or associated with importations from other countries, particularly countries in Europe where several outbreaks are ongoing. Persons younger than 20 years of age accounted for 76% of the cases; 91% were in persons who were unvaccinated (most because of personal or religious beliefs) or of unknown vaccination status. The increase in the number of cases of measles in 2008 was not a result of a greater

number of imported measles cases. It was the result of more measles transmission after the virus was imported. The importation-associated cases occurred largely among school-aged children who were eligible for vaccination but whose parents chose not to have them vaccinated. Many of these children were home-schooled and not subject to school entry vaccination requirements.

Classification of Measles Cases

Clinical Classification of Measles Cases

A suspect case is defined as a febrile illness accompanied by a generalized maculopapular rash.

A probable case meets the measles case definition of generalized maculopapular rash lasting 3 days or longer, with fever (101°F [38.3°C] or higher), which is accompanied by cough, coryza, or conjunctivitis and has no or noncontributory serologic or virologic testing and is not epidemiologically linked to a confirmed case. A confirmed case meets the case definition and is epidemiologically linked to another confirmed or probable case or is laboratory confirmed. A laboratory-confirmed case does not need to meet the clinical case definition.

Only confirmed cases should be reported to CDC, but both confirmed and probable cases should be reported as soon as possible to the local or state health department.

Measles Clinical Case Definition

- Generalized rash lasting 3 days or longer, and
- Temperature 101°F (38.3°C) or higher, and
- Cough or coryza or conjunctivitis

Epidemiologic Classification

An international imported case has its source outside the country, rash onset occurs within 21 days after entering the country, and illness cannot be linked to local transmission.

An indigenous case is any case that cannot be proved to be imported. Subclasses of indigenous cases exist; for more information, see CDC Manual for Surveillance of Vaccine-Preventable Diseases (available on the CDC website at http://www.cdc.gov/pubs/surv-manual/default.htm).

Measles Vaccine

Measles virus was first isolated by John Enders in 1954. The first measles vaccines were licensed in 1963. In that year, both an inactivated ("killed") and a live attenuated vaccine (Edmonston B strain) were licensed for use in the United States. The inactivated vaccine was withdrawn in 1967 because it did not protect against measles virus infection. Furthermore, recipients of inactivated measles vaccine frequently developed a unique syndrome, atypical measles, if they were infected with wild-type measles virus (see Atypical Measles, above). The original Edmonston B vaccine was withdrawn in 1975 because of a relatively high

Measles Vaccines

1963	Killed and live attenuated vaccines
1965	Live further attenuated vaccine
1967	Killed vaccine withdrawn
1968	Live further attenuated vaccine (Edmonston-Enders strain)
1971	Licensure of combined measles-mumps-rubella vaccine
1989	Two-dose schedule
2005	Licensure of combined measles-mumps-rubella-varicella vaccine

frequency of fever and rash in recipients. A live, further attenuated vaccine (Schwarz strain) was first introduced in 1965 but also is no longer used in the United States. Another live, further attenuated strain vaccine (Edmonston-Enders strain) was licensed in 1968. These further attenuated vaccines caused fewer reactions than the original Edmonston B vaccine.

Measles Vaccine

- Composition: Live virus
- Efficacy: 95% (range, 90%-98%)
- Duration of Immunity: Lifelong
- Schedule: 2 doses
- Should be administered with mumps and rubella as MMR or with mumps, rubella and varicella as MMRV

Characteristics

The only measles virus vaccine now available in the United States is a live, more attenuated Edmonston-Enders strain (formerly called "Moraten"). The vaccine is available combined with mumps and rubella vaccines as MMR, or combined with mumps, rubella, and varicella vaccine as MMRV (ProQuad). The Advisory Committee on Immunization Practices (ACIP) recommends that MMR be used when any of the individual components is indicated. Use of single-antigen measles vaccine is not recommended.

Measles vaccine is prepared in chick embryo fibroblast tissue culture. MMR and MMRV are supplied as a lyophylized (freeze-dried) powder and are reconstituted with sterile, preservative-free water. The vaccines contain a small amount of human albumin, neomycin, sorbitol, and gelatin.

MMR Vaccine Failure

- Measles, mumps, or rubella disease (or lack of immunity) in a previously vaccinated person
- 2%-5% of recipients do not respond to the first dose
- Caused by antibody, damaged vaccine, incorrect records
- Most persons with vaccine failure will respond to second dose

Immunogenicity and Vaccine Efficacy

Measles vaccine produces an inapparent or mild, noncommunicable infection. Measles antibodies develop in approximately 95% of children vaccinated at 12 months of age and 98% of children vaccinated at 15 months of age. Seroconversion rates are similar for single-antigen measles vaccine, MMR, and MMRV. Approximately 2%–5% of children who receive only one dose of MMR vaccine fail to respond to it (i.e., primary vaccine failure). MMR vaccine failure may occur because of passive antibody in the vaccine recipient, damaged vaccine, incorrect records, or possibly other reasons. Most persons who fail to respond to the first dose will respond to a second dose. Studies indicate that more than 99% of persons who receive two doses of measles vaccine (with the first dose administered no earlier than the first birthday) develop serologic evidence of measles immunity.

Although the titer of vaccine-induced antibodies is lower than that following natural disease, both serologic and epidemiologic evidence indicate that vaccine-induced immunity appears to be long-term and probably lifelong in most persons. Most vaccinated persons who appear to lose antibody show an anamnestic immune response upon revaccination, indicating that they are probably still immune. Although revaccination can increase antibody

titer in some persons, available data indicate that the increased titer may not be sustained. Some studies indicate that secondary vaccine failure (waning immunity) may occur after successful vaccination, but this appears to occur rarely and to play only a minor role in measles transmission and outbreaks.

Vaccination Schedule and Use

Two doses of measles vaccine, as combination MMR, separated by at least 4 weeks, are routinely recommended for all children. All persons born during or after 1957 should have documentation of at least one dose of MMR or other evidence of measles immunity (see below). Certain adolescents and adults should receive two doses of MMR.

The first dose of MMR should be given on or after the first birthday. Any dose of measles-containing vaccine given before 12 months of age should not be counted as part of the series. Children vaccinated with measles-containing vaccine before 12 months of age should be revaccinated with two doses of MMR vaccine, the first of which should be administered when the child is at least 12 months of age.

A second dose of MMR is recommended to produce immunity in those who failed to respond to the first dose. The second dose of MMR vaccine should routinely be given at age 4–6 years, before a child enters kindergarten or first grade. The recommended visit at age 11 or 12 years can serve as a catch-up opportunity to verify vaccination status and administer MMR vaccine to those children who have not yet received two doses of MMR.

The second dose of MMR may be administered as soon as 1 month (i.e., minimum of 28 days) after the first dose. Children who have already received two doses of MMR vaccine at least 4 weeks apart, with the first dose administered no earlier than the first birthday, do not need an additional dose when they enter school. Children without documentation of adequate vaccination against measles, mumps, and rubella or other acceptable evidence of immunity to these diseases when they enter school should be admitted after receipt of the first dose of MMR. A second dose should be administered as soon as possible, but no less than 4 weeks after the first dose.

Only doses of vaccine with written documentation of the date of receipt should be accepted as valid. Self-reported doses or a parental report of vaccination is not considered adequate documentation. A healthcare provider should not provide an immunization record for a patient unless that healthcare provider has administered the vaccine or has seen a record that documents vaccination. Persons who lack adequate documentation of vaccination or other acceptable evidence of immunity should be vaccinated. Vaccination

Measles (MMR) Vaccine Indications

- All children 12 months of age and older
- Susceptible adolescents and adults without documented evidence of immunity

Measles-Mumps-Rubella Vaccine

- 12 months is the recommended and minimum age
- MMR given before 12 months should not be counted as a valid dose
- Revaccinate at 12 months of age or older

Second Dose of Measles Vaccine

- Intended to produce measles immunity in persons who failed to respond to the first dose (primary vaccine failure)
- May boost antibody titers in some persons

Second Dose of Measles Vaccine

- First dose of MMR at 12-15 months
- Second dose of MMR at 4-6 years
- Second dose may be given any time at least 4 weeks after the first dose

status and receipt of all vaccinations should be documented in the patient's permanent medical record and in a vaccination record held by the individual.

MMRV is approved by the Food and Drug Administration for children 12 months through 12 years of age (that is, until the 13th birthday). MMRV should not be administered to persons 13 years of age or older.

Vaccination of Adults

Adults born in 1957 or later who do not have a medical contraindication should receive at least one dose of MMR vaccine unless they have documentation of vaccination with at least one dose of measles-, mumps- and rubella-containing vaccine or other acceptable evidence of immunity to these three diseases. With the exception of women who might become pregnant (see Chapter 18, Rubella) and persons who work in medical facilities, birth before 1957 generally can be considered acceptable evidence of immunity to measles, mumps, and rubella.

Adults at Increased Risk of Measles

- College students
- International travelers
- Healthcare personnel

Certain groups of adults may be at increased risk for exposure to measles and should receive special consideration for vaccination. These include persons attending colleges and other post-high school educational institutions, persons working in medical facilities, and international travelers.

Colleges and other post-high school educational institutions are potential high- risk areas for measles, mumps, and rubella transmission because of large concentrations of susceptible persons. Prematriculation vaccination requirements for measles immunity have been shown to significantly decrease the risk of measles outbreaks on college campuses where they are implemented and enforced. Colleges, universities, technical and vocational schools, and other institutions for post-high school education should require documentation of two doses of MMR vaccine or other acceptable evidence of measles, mumps, and rubella immunity before entry.

Students who have no documentation of live measles, mumps, or rubella vaccination or other acceptable evidence of measles, mumps, and rubella immunity at the time of enrollment should be admitted to classes only after receiving the first dose of MMR. A second dose of MMR should be administered no less than 4 weeks (i.e., minimum of 28 days) later. Students with evidence of prior receipt of only one dose of MMR or other measles-containing vaccine on or after their first birthday should receive a second dose of MMR, provided at least 4 weeks have elapsed since their previous dose.

Measles Immunity in Healthcare Personnel

- All persons who work within medical facilities should have evidence of immunity to measles

Persons who work in medical facilities are at higher risk for exposure to measles than the general population. All persons who work within medical facilities should have evidence of immunity to measles, mumps, and rubella. Because any

healthcare personnel (i.e., medical or nonmedical, paid or volunteer, full time or part time, student or nonstudent, with or without patient-care responsibilities) who is susceptible to measles or rubella can contract and transmit these diseases, all medical facilities (i.e., inpatient and outpatient, private and public) should ensure measles and rubella immunity among those who work within their facilities. (A possible exception might be a facility that treats only elderly patients considered at low risk for measles and rubella and their complications.)

Adequate vaccination for measles, mumps, and rubella for healthcare personnel born during or after 1957 consists of two doses of a live measles- and mumps-containing vaccine and at least one dose of a live rubella-containing vaccine. Healthcare personnel needing a second dose of measles-containing vaccine should be revaccinated at least 4 weeks after their first dose.

Although birth before 1957 is generally considered acceptable evidence of measles, mumps, and rubella immunity, medical facilities should consider recommending a dose of MMR vaccine to unvaccinated personnel born before 1957 who do not have a history of prior measles disease or laboratory evidence of measles immunity, and to those without laboratory evidence of rubella immunity.

Serologic screening need not be done before vaccinating for measles and rubella unless the medical facility considers it cost-effective. Serologic testing is appropriate only if tracking systems are used to ensure that tested persons who are identified as susceptible are subsequently vaccinated in a timely manner. Serologic testing for immunity to measles and rubella is not necessary for persons documented to be appropriately vaccinated or who have other acceptable evidence of immunity. If the return and timely vaccination of those screened cannot be assured, serologic testing before vaccination should not be done.

Persons who travel outside the United States are at increased risk of exposure to measles. Measles is endemic or epidemic in many countries throughout the world. Although proof of immunization is not required for entry into the United States or any other country, persons traveling or living abroad should have evidence of measles immunity. Adequate vaccination of persons who travel outside the United States is two doses of MMR.

Revaccination

Revaccination is recommended for certain persons. The following groups should be considered unvaccinated and should receive at least one dose of measles vaccine: persons 1) vaccinated before the first birthday, 2) vaccinated with killed measles vaccine (KMV), 3) vaccinated with KMV followed by live vaccine less than 4 months after the last

Measles Vaccine Indications for Revaccination

- Vaccinated before the first birthday
- Vaccinated with killed measles vaccine
- Vaccinated prior to 1968 with an unknown type of vaccine
- Vaccinated with IG in addition to a further attenuated strain or vaccine of unknown type

dose of KMV, 4) vaccinated before 1968 with an unknown type of vaccine (the vaccine may have been KMV), or 5) vaccinated with IG in addition to a further attenuated strain or vaccine of unknown type. (Revaccination is not necessary if IG was given with Edmonston B vaccine.)

Postexposure Prophylaxis

Live measles vaccine provides permanent protection and may prevent disease if given within 72 hours of exposure. Immune globulin (IG) may prevent or modify disease and provide temporary protection if given within 6 days of exposure. The dose is 0.25 mL/kg body weight, with a maximum of 15 mL intramuscularly. The recommended dose of IG for immunocompromised persons is 0.5mL/kg of body weight (maximum 15 mL) intramuscularly. IG may be especially indicated for susceptible household contacts of measles patients, particularly contacts younger than 1 year of age (for whom the risk of complications is highest). If the child is 12 months of age or older, live measles vaccine should be given about 5 months later when the passive measles antibodies have waned. IG should not be used to control measles outbreaks.

Contraindications and Precautions to Vaccination

Persons who have experienced a severe allergic reaction (anaphylaxis) to a vaccine component or following a prior dose of measles vaccine should generally not be vaccinated with MMR.

MMR Vaccine Contraindications and Precautions

- Severe allergic reaction to vaccine component or following prior dose
- Pregnancy
- Immunosuppression
- Moderate or severe acute illness
- Recent blood product

In the past, persons with a history of anaphylactic reactions following egg ingestion were considered to be at increased risk for serious reactions after receipt of measles- or mumps-containing vaccines, which are produced in chick embryo fibroblasts. However, data suggest that anaphylactic reactions to measles- and mumps-containing vaccines are not associated with hypersensitivity to egg antigens but to other components of the vaccines (such as gelatin). The risk for serious allergic reactions following receipt of these vaccines by egg-allergic persons is extremely low, and skin-testing with vaccine is not predictive of allergic reaction to vaccination. Therefore, MMR may be administered to egg-allergic children without prior routine skin testing or the use of special protocols.

Measles and Mumps Vaccines and Egg Allergy

- Measles and mumps viruses grown in chick embryo fibroblast culture
- Studies have demonstrated safety of MMR in egg-allergic children
- Vaccinate without testing

MMR vaccine does not contain penicillin. A history of penicillin allergy is not a contraindication to vaccination with MMR or any other U.S. vaccine.

Women known to be pregnant should not receive measles vaccine. Pregnancy should be avoided for 4 weeks following MMR vaccine. Close contact with a pregnant

woman is NOT a contraindication to MMR vaccination of the contact. Breastfeeding is NOT a contraindication to vaccination of either the woman or the breastfeeding child.

Replication of vaccine viruses can be prolonged in persons who are immunosuppressed or immunodeficient. Severe immunosuppression can be due to a variety of conditions, including congenital immunodeficiency, HIV infection, leukemia, lymphoma, generalized malignancy, or therapy with alkylating agents, antimetabolites, radiation, or large doses of corticosteroids. Evidence based on case reports has linked measles vaccine virus infection to subsequent death in at least six severely immunocompromised persons. For this reason, patients who are severely immunocompromised for any reason should not be given MMR vaccine. Healthy susceptible close contacts of severely immunocompromised persons should be vaccinated.

In general, persons receiving large daily doses of corticosteroids (2 mg/kg or more per day, or 20 mg or more per day of prednisone) for 14 days or more should not receive MMR vaccine because of concern about vaccine safety. MMR and its component vaccines should be avoided for at least 1 month after cessation of high-dose therapy. Persons receiving low-dose or short-course (less than 14 days) therapy, alternate-day treatment, maintenance physiologic doses, or topical, aerosol, intra-articular, bursal, or tendon injections may be vaccinated. Although persons receiving high doses of systemic corticosteroids daily or on alternate days during an interval of less than 14 days generally can receive MMR or its component vaccines immediately after cessation of treatment, some experts prefer waiting until 2 weeks after completion of therapy.

Patients with leukemia in remission who have not received chemotherapy for at least 3 months may receive MMR or its component vaccines.

Measles disease may be severe in persons with HIV infection. Available data indicate that vaccination with MMR has not been associated with severe or unusual adverse reactions in HIV-infected persons without evidence of severe immunosuppression, although antibody responses have been variable. MMR vaccine is recommended for all asymptomatic HIV-infected persons and should be considered for symptomatic persons who are not severely immunosuppressed. Asymptomatic children do not need to be evaluated and tested for HIV infection before MMR or other measles-containing vaccines are administered. A theoretical risk of an increase (probably transient) in HIV viral load following MMR vaccination exists because such an effect has been observed with other vaccines. The clinical significance of such an increase is not known.

Measles Vaccine and HIV Infection

- MMR recommended for persons with asymptomatic and mildly symptomatic HIV infection
- NOT recommended for those with evidence of severe immunosuppression
- Prevaccination HIV testing not recommended

MMR and other measles-containing vaccines are not recommended for HIV-infected persons with evidence of severe immunosuppression (see table). MMRV is not approved for and should not be administered to a person known to be infected with HIV.

Persons with moderate or severe acute illness should not be vaccinated until the illness has improved. This precaution is intended to prevent complicating the management of an ill patient with a potential vaccine adverse reaction, such as fever. Minor illness (e.g., otitis media, mild upper respiratory infections), concurrent antibiotic therapy, and exposure to or recovery from other illness are not contraindications to measles vaccination.

Age-specific CD4+ T-lymphocyte count and percent of total lymphocytes as criteria for severe immunosuppression in HIV-infected persons.

Criteria	age <12 months	age 1-5 years	age 6-12 years	age ≥13 years
Total CD4+ T-lymphocytes	<750 per μL	<500 per μL	<200 per μL	<200 per μL
OR	**OR**	**OR**	**OR**	**OR**
CD4+ T-lymphocytes (as % of total lymphocytes)	<15%	<15%	<15%	<14%

Receipt of antibody-containing blood products (e.g., immune globulin, whole blood or packed red blood cells, intravenous immune globulin) may interfere with seroconversion after measles vaccine. The length of time that such passively acquired antibody persists depends on the concentration and quantity of blood product received. For instance, it is recommended that vaccination be delayed for 3 months following receipt of immune globulin for prophylaxis of hepatitis A; a 7 to 11 month delay is recommended following administration of intravenous immune globulin, depending on the dose. For more information, see Chapter 2, General Recommendations on Immunization, and the table in Appendix A.

Persons who have a history of thrombocytopenic purpura or thrombocytopenia (low platelet count) may be at increased risk for developing clinically significant thrombocytopenia after MMR vaccination. No deaths have been reported as a direct consequence of vaccine-induced thrombocytopenia. The decision to vaccinate with MMR depends on the benefits of immunity to measles, mumps, and rubella and the risks for recurrence or exacerbation of thrombocytopenia after vaccination or during natural infection with measles or rubella. The benefits of immunization are usually greater than the potential risks, and administration of MMR vaccine is justified because of the even greater risk for thrombocy-

topenia after measles or rubella disease. However, deferring a subsequent dose of MMR vaccine may be prudent if the previous episode of thrombocytopenia occurred within 6 weeks after the previous dose of the vaccine. Serologic evidence of measles immunity in such persons may be sought in lieu of MMR vaccination.

Tuberculin skin testing (TST) is not a prerequisite for vaccination with MMR or other measles-containing vaccine. TST has no effect on the response to MMR vaccination. However, measles vaccine (and possibly mumps, rubella, and varicella vaccines) may transiently suppress the response to TST in a person infected with *Mycobacterium tuberculosis*. If tuberculin skin testing is needed at the same time as administration of measles-containing vaccine, TST and vaccine can be administered at the same visit. Simultaneously administering TST and measles-containing vaccine does not interfere with reading the TST result at 48–72 hours and ensures that the person has received measles vaccine. If the measles-containing vaccine has been administered recently, TST screening should be delayed at least 4 weeks after vaccination. A delay in administering TST will remove the concern of any theoretical suppression of TST reactivity from the vaccine. TST screening can be performed and read before administering the measles-containing vaccine. This option is the least favored because it will delay receipt of the vaccine.

Tuberculin Skin Testing (TST)* and Measles Vaccine

- Apply TST at same visit as MMR
- Delay TST at least 4 weeks if MMR given first
- Apply TST first and administer MMR when skin test read (least favored option because receipt of MMR is delayed)

*previously called PPD

Adverse Reactions Following Vaccination

Adverse reactions following measles vaccine (except allergic reactions) represent replication of measles vaccine virus with subsequent mild illness. These events occur 5 to 12 days postvaccination and only in persons who are susceptible to infection. There is no evidence of increased risk of adverse reactions following MMR vaccination in persons who are already immune to the diseases.

MMR Adverse Reactions

• Fever	5%-15%
• Rash	5%
• Joint symptoms	25%
• Thrombocytopenia	<1/30,000 doses
• Parotitis	rare
• Deafness	rare
• Encephalopathy	<1/1,000,000 doses

Fever is the most common adverse reaction following MMR vaccination. Although measles, mumps, and rubella vaccines may cause fever after vaccination, the measles component of MMR vaccine is most often associated with this adverse reaction. After MMR vaccination, 5% to 15% of susceptible persons develop a temperature of 103°F (39.4°C) or higher, usually occurring 7 to 12 days after vaccination and generally lasting 1 or 2 days. Most persons with fever are otherwise asymptomatic.

Measles- and rubella-containing vaccines, including MMR, may cause a transient rash. Rashes, usually appearing 7 to 10 days after MMR or measles vaccination, have been reported in approximately 5% of vaccinees.

Rarely, MMR vaccine may cause thrombocytopenia within 2 months after vaccination. Estimates of the frequency of

clinically apparent thrombocytopenia from Europe are one case per 30,000–40,000 vaccinated susceptible persons, with a temporal clustering of cases occurring 2 to 3 weeks after vaccination. The clinical course of these cases was usually transient and benign, although hemorrhage occurred rarely. The risk for thrombocytopenia during rubella or measles infection is much greater than the risk after vaccination. Based on case reports, the risk for MMR-associated thrombocytopenia may be higher for persons who have previously had immune thrombocytopenic purpura, particularly for those who had thrombocytopenic purpura after an earlier dose of MMR vaccine.

Transient lymphadenopathy sometimes occurs following receipt of MMR or other rubella-containing vaccine, and parotitis has been reported rarely following receipt of MMR or other mumps-containing vaccine.

Arthralgias and other joint symptoms are reported in up to 25% of susceptible adult women given MMR vaccine. This adverse reaction is associated with the rubella component (see Chapter 18, Rubella, for more details). Allergic reactions following the administration of MMR or any of its component vaccines are rare. Most of these reactions are minor and consist of a wheal and flare or urticaria at the injection site. Immediate, anaphylactic reactions to MMR or its component vaccines are extremely rare. Allergic reactions including rash, pruritus, and purpura have been temporally associated with mumps vaccination, but these are uncommon and usually mild and of brief duration.

To date there is no convincing evidence that any vaccine causes autism or autism spectrum disorder. Concern has been raised about a possible relation between MMR vaccine and autism by some parents of children with autism. Symptoms of autism are often noticed by parents during the second year of life, and may follow administration of MMR by weeks or months. Two independent nongovernmental groups, the Institute of Medicine (IOM) and the American Academy of Pediatrics (AAP), have reviewed the evidence regarding a potential link between autism and MMR vaccine. Both groups independently concluded that available evidence does not support an association, and that the United States should continue its current MMR vaccination policy. Additional research on the cause of autism is needed.

Vaccine Storage and Handling

Measles vaccine and MMR must be shipped with refrigerant to maintain a temperature of 50°F (10°C) or less at all times. Vaccine must be refrigerated immediately on arrival and protected from light at all times. The vaccine must be stored at refrigerator temperature (35°–46°F [2°–8°C]), but may be frozen. Diluent may be stored at refrigerator temperature or at room temperature. MMRV must be shipped to maintain a

temperature of -4°F (-20°C) or less at all times. MMRV must be stored at an average temperature of 5°F (-15°C) or less at all times.

After reconstitution, measles and MMR vaccines must be stored at refrigerator temperature and protected from light. Reconstituted vaccine should be used immediately. If reconstituted vaccine is not used within 8 hours, it must be discarded. MMRV must be administered within 30 minutes of reconstitution.

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Meningococcal Disease

Meningococcal disease is an acute, potentially severe illness caused by the bacterium *Neisseria meningitidis*. Illness believed to be meningococcal disease was first reported in the 16th century. The first definitive description of the disease was by Vieusseux in Switzerland in 1805. The bacterium was first identified in the spinal fluid of patients by Weichselbaum in 1887.

Neisseria meningitidis is a leading cause of bacterial meningitis and sepsis in the United States. It can also cause focal disease, such as pneumonia and arthritis. *N. meningitidis* is also a cause of epidemics of meningitis and bacteremia in sub-Saharan Africa. The World Health Organization has estimated that meningococcal disease was the cause of 171,000 deaths worldwide in 2000.

The first monovalent (group C) polysaccharide vaccine was licensed in the United States in 1974. A quadrivalent polysaccharide vaccine was licensed in 1978. Meningococcal conjugate vaccine has been licensed in United Kingdom since 1999 and has had a major impact on the incidence of type C meningococcal disease. A quadrivalent conjugate vaccine was first licensed in the United States in 2005.

Neisseria meningitidis

- Severe acute bacterial infection
- Cause of meningitis, sepsis, and focal infections
- Epidemic disease in sub-Saharan Africa
- Current polysaccharide vaccine licensed in 1978
- Conjugate vaccine licensed in 2005

Neisseria meningitidis

N. meningitidis, or meningococcus, is an aerobic, gram-negative diplococcus, closely related to *N. gonorrhoeae*, and to several nonpathogenic *Neisseria* species, such as *N. lactamica*. The organism has both an inner (cytoplasmic) and outer membrane, separated by a cell wall. The outer membrane contains several protein structures that enable the bacteria to interact with the host cells as well as perform other functions.

The outer membrane is surrounded by a polysaccharide capsule that is necessary for pathogenicity because it helps the bacteria resist phagocytosis and complement-mediated lysis. The outer membrane proteins and the capsular polysaccharide make up the main surface antigens of the organism.

Meningococci are classified by using serologic methods based on the structure of the polysaccharide capsule. Thirteen antigenically and chemically distinct polysaccharide capsules have been described. Some strains, often those found to cause asymptomatic nasopharyngeal carriage, are not groupable and do not have a capsule. Almost all invasive disease is caused by one of five serogroups: A, B, C, Y, and W-135. The relative importance of each serogroup depends on geographic location, as well as other factors, such as age. For instance, serogroup A is a major cause of

Neisseria meningitidis

- Aerobic gram-negative bacteria
- At least 13 serogroups based on characteristics of the polysaccharide capsule
- Most invasive disease caused by serogroups A, B, C, Y, and W-135
- Relative importance of serogroups depends on geographic location and other factors (e.g. age)

disease in sub-Saharan Africa but is rarely isolated in the United States.

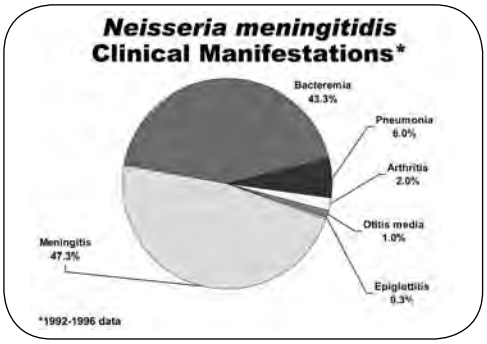
Meningococci are further classified on the basis of certain outer membrane proteins. Molecular subtyping using specialized laboratory techniques (e.g., pulsed-field gel electrophoresis) can provide useful epidemiologic information.

Meningococcal Disease Pathogenesis

- Organism colonizes nasopharynx
- In some persons organism invades bloodstream and causes infection at distant site
- Antecedent URI may be a contributing factor

Pathogenesis

Meningococci are transmitted by droplet aerosol or secretions from the nasopharynx of colonized persons. The bacteria attach to and multiply on the mucosal cells of the nasopharynx. In a small proportion (less than 1%) of colonized persons, the organism penetrates the mucosal cells and enters the bloodstream. The bacteria spread by way of the blood to many organs. In about 50% of bacteremic persons, the organism crosses the blood–brain barrier into the cerebrospinal fluid and causes purulent meningitis. An antecedent upper respiratory infection may be a contributing factor.



Clinical Features

The incubation period of meningococcal disease is 3 to 4 days, with a range of 2 to 10 days.

Meningitis is the most common presentation of invasive meningococcal disease and results from hematogenous dissemination of the organism. Meningeal infection is similar to other forms of acute purulent meningitis, with sudden onset of fever, headache, and stiff neck, often accompanied by other symptoms, such as nausea, vomiting, photophobia (eye sensitivity to light), and altered mental status. Meningococci can be isolated from the blood in up to 75% of persons with meningitis.

Meningococcal Meningitis

- Most common pathologic presentation
- Result of hematogenous dissemination
- Clinical findings
  - —fever
  - —headache
  - —stiff neck

Meningococcal sepsis (bloodstream infection or meningococcemia) occurs without meningitis in 5% to 20% of invasive meningococcal infections. This condition is characterized by abrupt onset of fever and a petechial or purpuric rash, often associated with hypotension, shock, acute adrenal hemorrhage, and multiorgan failure.

Meningococcemia

- Bloodstream infection
- May occur with or without meningitis
- Clinical findings
  - —fever
  - —petechial or purpuric rash
  - —hypotension
  - —multiorgan failure

Less common presentations of meningococcal disease include pneumonia (5% to 15% of cases), arthritis (2%), otitis media (1%), and epiglottitis (less than 1%).

The case-fatality rate of invasive meningococcal disease is 9% to 12%, even with appropriate antibiotic therapy. The fatality rate of meningococcemia is up to 40%. As many as 20% of survivors have permanent sequelae, such as hearing loss, neurologic damage, or loss of a limb.

Risk factors for the development of meningococcal disease include deficiencies in the terminal common complement

pathway and functional or anatomic asplenia. Persons with HIV infection are probably at increased risk for meningococcal disease. Certain genetic factors (such as polymorphisms in the genes for mannose-binding lectin and tumor necrosis factor) may also be risk factors.

Family members of an infected person are at increased risk for meningococcal disease. Antecedent upper respiratory tract infection, household crowding, and both active and passive smoking also are also associated with increased risk. In the United States, African Americans and persons of low socioeconomic status have been consistently at higher risk; however, race and low socioeconomic status are likely markers for differences in factors such as household crowding rather than risk factors. During outbreaks, bar or nightclub patronage and alcohol use have also been associated with higher risk for disease.

Cases of invasive meningococcal disease, including at least two fatal cases, have been reported among microbiologists. These persons have worked with *N. meningitidis* isolates rather than patient specimens.

Studies have shown that college freshmen living in dormitories are at modestly increased risk of meningococcal disease. However, U.S. college students are not at higher risk for meningococcal disease than other persons of similar age.

Laboratory Diagnosis

Invasive meningococcal disease is typically diagnosed by isolation of *N. meningitidis* from a normally sterile site. However, sensitivity of bacterial culture may be low, particularly when performed after initiation of antibiotic therapy. A Gram stain of cerebrospinal fluid showing gram-negative diplococci strongly suggests meningococcal meningitis.

Kits to detect polysaccharide antigen in cerebrospinal fluid are rapid and specific, but false-negative results are common, particularly in serogroup B disease. Antigen tests of urine or serum are unreliable.

Serologic testing (e.g., enzyme immunoassay) for antibodies to polysaccharide may be used as part of the evaluation if meningococcal disease is suspected but should not be used to establish the diagnosis.

Medical Management

The clinical presentation of meningococcal meningitis is similar to other forms of bacterial meningitis. Consequently, empiric therapy with broad-spectrum antibiotics (e.g., third-generation cephalosporin, vancomycin) should be started promptly after appropriate cultures have been obtained.

Neisseria meningitidis
Risk Factors for Invasive Disease

- Host factors
  - terminal complement pathway deficiency
  - asplenia
  - genetic risk factors
- Exposure factors
  - household exposure
  - concurrent upper respiratory tract infection
  - demographic and socioeconomic factors and crowding
  - active and passive smoking

Meningococcal Disease Among Young Adults, United States, 1998-1999

•18-23 years old	1.4 /100,000
•18-23 years old not college student	1.4 /100,000
•Freshmen	1.9 /100,000
•Freshmen in dorm	5.1 /100,000

Bruce et al, *JAMA* 2001;286:688-93

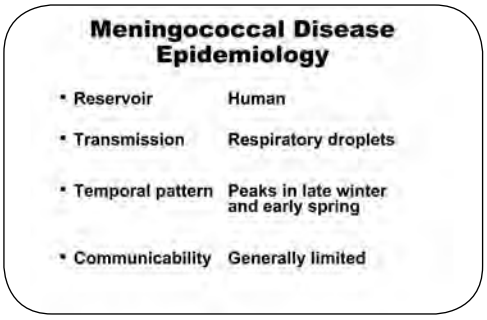
Meningococcal Disease
Laboratory Diagnosis

- Bacterial culture
- Gram stain
- Non-culture methods
  - —antigen detection in CSF
  - —serology

Neisseria meningitidis
Medical Management

- Initial empiric antibiotic treatment after appropriate cultures are obtained
- Treatment with penicillin alone recommended after confirmation of *N. meningitidis*

Many antibiotics are effective for *N. meningitidis* infection, including penicillin. Few penicillin-resistant strains of meningococcus have been reported in the United States. Once *N. meningitidis* infection has been confirmed, penicillin alone is recommended.



Epidemiology

Occurrence

Meningococcal disease occurs worldwide in both endemic and epidemic form.

Reservoir

Humans are the only natural reservoir of meningococcus. As many as 10% of adolescents and adults are asymptomatic transient carriers of *N. meningitidis*, most strains of which are not pathogenic (i.e., strains that are not groupable).

Transmission

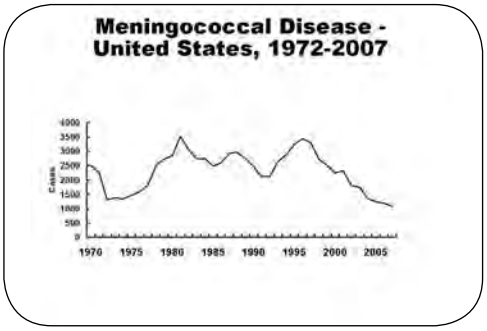
Primary mode is by respiratory droplet spread or by direct contact.

Temporal Pattern

Meningococcal disease occurs throughout the year, However, the incidence is highest in the late winter and early spring.

Communicability

The communicability of *N. meningitidis* is generally limited. In studies of households in which a case of meningococcal disease has occurred, only 3%–4% of households had secondary cases. Most households had only one secondary case. Estimates of the risk of secondary transmission are generally 2–4 cases per 1,000 household members at risk. However, this risk is 500–800 times that in the general population.



Secular Trends in the United States

Approximately 1,000 to 3,000 cases of meningococcal disease are reported each year in the United States (0.4–1.3 cases per 100,000 population). In 2004, an estimated 125 deaths due to meningococcal disease occurred in the United States. Infants younger than 12 months of age have the highest rates of disease. Incidence of disease declines in early childhood, increases during adolescence and early adulthood, then declines among older adults. The rate of invasive disease among persons 17–20 years of age is approximately twice that of the overall U.S. population. Although incidence is relatively low, more cases occur in

persons 23–64 years of age than in any other age group. The proportion of cases among adolescents and young adults has increased in recent years. During 1992–1998, 28% of reported case-patients were 12–29 years of age.

The proportion of disease caused by different serogroups has changed during the last 15 years. From 1988 to 1991, most cases of meningococcal disease in the United States were due to either serogroup C or B, and serogroup Y accounted for only 2% of cases. However, during 1996–2001, serogroup Y accounted for 21% of cases, with serogroups B and C accounting for 31% and 42%, respectively. Nongroupable strains accounted for 5% of cases. The proportion of cases caused by each serogroup also varies by age group. In 2001, 65% of cases among infants aged less than 1 year were caused by serogroup B, for which no vaccine is available in the United States. Among persons 18–34 years of age, 41% of cases were due to serogroup B, and 25% and 14% were due to serogroups C and Y, respectively.

In the United States, meningococcal outbreaks account for less than 5% of reported cases (95%–97% of cases are sporadic). However, since 1991, the frequency of localized outbreaks has increased. Most of these outbreaks have been caused by serogroup C. Since 1997, localized outbreaks caused by serogroups Y and B have also been reported. See http://www.cdc.gov/mmwr/PDF/rr/rr4605.pdf for additional information on the evaluation and management of meningococcal outbreaks.

Large outbreaks of serogroup A meningococcal disease occur in the African "meningitis belt," an area that extends from Ethiopia to Senegal. Rates of endemic meningococcal disease in this area are several times higher than in industrialized countries. In addition, outbreaks occur every 8–12 years with attack rates of 500–1000 cases per 100,000 population.

Meningococcal Vaccines

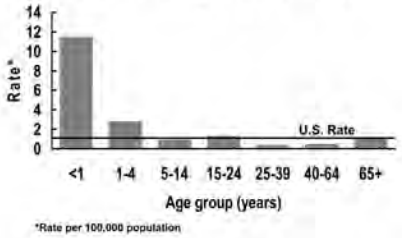
Characteristics

Meningococcal Polysaccharide Vaccine (MPSV4)

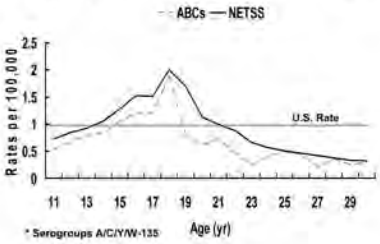
The first meningococcal polysaccharide vaccine was licensed in the United States in 1974. The current quadrivalent A, C, Y, W-135 polysaccharide vaccine (Menomune, sanofi pasteur) was licensed in 1978. Each dose consists of 50 mcg of each of the four purified bacterial capsular polysaccharides. The vaccine contains lactose as a stabilizer.

MPSV4 is administered by subcutaneous injection. The vaccine is available in single-dose and 10-dose vials. Fifty-dose vials are no longer available. Diluent for the

Meningococcal Disease, 1998 Incidence by Age Group



Rates of Meningococcal Disease* by Age, United States, 1991-2002



Meningococcal Disease in the United States

- Distribution of cases by serogroup varies by time and age group
- In 1996-2001:
  - –21% serogroup Y
  - –31% serogroup B
  - –42% serogroup C
  - –65% of cases among children <1 year of age due to serogroup B

Meningococcal Outbreaks in the United States

- Outbreaks account for <5% of reported cases
- Frequency of localized outbreaks has increased since 1991
- Most recent outbreaks caused by serogroup C
- Since 1997 outbreaks caused by serogroup Y and B organisms have also been reported

Meningococcal Polysaccharide Vaccine (MPSV4)

- Menomune (sanofi pasteur)
- Quadrivalent polysaccharide vaccine (A, C, Y, W-135)
- Administered by subcutaneous injection
- 10-dose vial contains thimerosal as a preservative

single-dose vial is sterile water without preservative. Diluent for the 10-dose vial is sterile water with thimerosal added as a preservative. After reconstitution the vaccine is a clear colorless liquid.

No vaccine is available in the United States for serogroup B.

Meningococcal Conjugate Vaccine (MCV4)

- Menactra® (sanofi pasteur)
- Quadrivalent polysaccharide vaccine (A, C, Y, W-135) conjugated to diphtheria toxoid
- Administered by intramuscular injection
- Single-dose vials do not contain a preservative

Meningococcal Conjugate Vaccine (MCV44)

Meningococcal conjugate vaccine (Menactra, sanofi pasteur) was first licensed in the United States in 2005. The vaccine contains *N. meningiditis* serogroups A, C, Y and W-135 capsular polysaccharide antigens individually conjugated to diphtheria toxoid protein. Each 0.5-mL dose of vaccine is formulated in sodium phosphate buffered isotonic sodium chloride solution to contain 4 mcg each of meningococcal A, C, Y, and W-135 polysaccharides conjugated to approximately 48 mcg of diphtheria toxoid protein carrier.

MCV4 is administered by intramuscular injection. It is supplied as a liquid in a single-dose vial. The vaccine does not contain a preservative.

Immunogenicity and Vaccine Efficacy

Meningococcal Polysaccharide Vaccine

The characteristics of MPSV4 are similar to other polysaccharide vaccines (e.g., pneumococcal polysaccharide). The vaccine is generally not effective in children younger than 18 months of age. The response to the vaccine is typical of a T-cell independent antigen, with an age-dependent response, and poor immunogenicity in children younger than 2 years of age. In addition, little boost in antibody titer occurs with repeated doses; the antibody which is produced is relatively low-affinity IgM, and "switching" from IgM to IgG production is poor.

A protective level of antibody is usually achieved within 7–10 days of vaccination. Among infants and children younger than 5 years of age, the level of antibody against serogroup A and C polysaccharide decreases substantially during the first 3 years following a single dose of vaccine. In healthy adults, antibody levels also decrease, but antibodies are detectable as long as 10 years after vaccination. Although vaccine-induced protection likely persists in school-aged children and adults for at least 3 years, the efficacy of the group A vaccine in children younger than 5 years of age may decrease markedly within this period. In one study, efficacy declined from more than 90% to less than 10% 3 years after vaccination among children who were younger than 4 years of age when vaccinated. Efficacy was 67% among children who were older than 4 years of age at vaccination.

Meningococcal Conjugate Vaccine

The approval of MCV4 was based on studies that compared the serologic response to a single dose to the response of persons of similar age who received a single dose of meningococcal polysaccharide vaccine. In these studies a similar proportion of recipients achieved at least a fourfold rise in serum bactericidal antibody titer assay following MCV4 as those who received MPSV4. The proportion of recipients in each group that achieved a titer of 1:128 (the titer considered to predict protection) was more than 98% in both groups.

Because the polysaccharides are conjugated to diphtheria toxoid for MCV4, it is believed that this vaccine will have a longer duration of protection than for MPSV4. In addition, MCV4 is expected to reduce asymptomatic carriage of *N. meningiditis* and produce "herd" immunity, as occurs for *Streptococcus pneumoniae* and *Haemophilus influenzae* type b following receipt of the respective conjugate vaccines. Pure polysaccharide vaccines have little or no effect on carriage of the vaccine organism.

Vaccination Schedule And Use

Meningococcal Polysaccharide Vaccine

For children 2 years of age and older and adults, MPSV4 is administered as a single 0.5-mL dose. The vaccine can be administered at the same time as other vaccines but should be given at a different anatomic site.

Routine vaccination of civilians with MPSV4 is not recommended because of its relative ineffectiveness in children younger than 2 years of age (the age group with the highest risk for sporadic disease) and because of its relatively short duration of protection. Use of MPSV4 should be limited to persons older than 55 years of age, or when MCV4 is not available.

Meningococcal Conjugate Vaccine

MCV4 is recommended for all children at 11 or 12 years of age. It is also recommended for all children 13 through 18 years of age who have not been previously vaccinated. Unvaccinated college freshmen who live in a dormitory should be vaccinated. Persons 2 through 55 years of age at increased risk of meningococcal disease should be vaccinated.

MCV4 is preferred for routine vaccination of adolescents and persons 2 through 55 years of age who are at increased risk of meningococcal disease. MPSV4 is an acceptable alternative for persons 2 through 55 years of age if MCV4 is not available.

Meningococcal vaccination is recommended for persons

at increased risk for meningococcal disease, including microbiologists who are routinely exposed to isolates of *N. meningitidis*, military recruits, persons who travel to and U.S. citizens who reside in countries in which *N. meningitidis* is hyperendemic or epidemic, persons with terminal complement component deficiency, and persons with functional or anatomic asplenia.

Meningococcal Vaccine Recommendations

- Recommended for persons at increased risk of meningococcal disease:
  - –microbiologists who are routinely exposed to isolates of *N. meningitidis*
  - –military recruits
  - –persons who travel to and U.S. citizens who reside in countries in which *N. meningitidis* is hyperendemic or epidemic
  - –terminal complement component deficiency
  - –functional or anatomic asplenia

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For travelers, vaccination is especially recommended for those visiting countries in the sub-Saharan Africa "meningitis belt" (Ethiopia in the east to Senegal in the west). Epidemics in the meningitis belt usually occur during the dry season (i.e., from December to June). Vaccination is recommended for travelers visiting the region during this time. Vaccination is required by the government of Saudi Arabia for all travelers to Mecca during the annual Hajj. Information concerning geographic areas for which vaccination is recommended can be obtained from the CDC Travelers Health website at http://www.cdc.gov/travel.

Meningococcal Endemic Areas 2004



MCV4 can be administered at the same visit as other indicated vaccines. All vaccines should be given at separate sites with separate syringes.

Both MCV4 and MPSV4 are recommended for use in control of meningococcal outbreaks caused by vaccine-preventable serogroups (A, C, Y, and W-135). An outbreak is defined by the occurrence of at least three confirmed or probable primary cases of serogroup C meningococcal disease during a period of 3 months or less, with a resulting primary attack rate of 10 or more cases per 100,000 population. For calculation of this threshold, population-based rates are used, and not age-specific attack rates, as have been calculated for college students. These recommendations are based on experience with serogroup C meningococcal outbreaks, but these principles may be applicable to outbreaks caused by the other vaccine-preventable meningococcal serogroups.

Meningococcal Vaccine Recommendations

- Both MCV4 and MPSV4 recommended for control of outbreaks caused by vaccine-preventable serogroups
- Outbreak definition:
  - –3 or more confirmed or probable primary cases
  - –period ≤3 months
  - –primary attack rate ≥10 cases per 100,000 population*

*Population-based rates should be used rather than age-specific attack rates

Revaccination

Revaccination may be indicated for persons previously vaccinated with MPSV4 who remain at increased risk for infection (e.g., persons residing in areas in which disease is epidemic), particularly for children who were first vaccinated when they were younger than 4 years of age. Such children should be considered for revaccination after 3 years if they remain at high risk. Although the need for revaccination of older children and adults after receiving MPSV4 has not been determined, antibody levels rapidly decline in 2–3 years, and if indications still exist for vaccination, revaccination may be considered 5 years after receipt of the first dose. MCV4 is recommended for revaccination of persons 2 through 55 years of age. However, use of MPSV4 is acceptable.

The Advisory Committee on Immunization Practices (ACIP) expects that MCV4 will provide longer protection than MPSV4. However, studies are needed to confirm this assumption. More data will likely become available within the next 5 years to guide recommendations on revaccination for persons who were previously vaccinated with MCV4. At the present time, revaccination after receipt of MCV4 is not recommended.

Contraindications and Precautions to Vaccination

For both MCV4 and MPSV4, a severe allergic (anaphylactic) reaction to a vaccine component or following a prior dose of either vaccine is a contraindication to receipt of further doses. A moderate or severe acute illness is reason to defer routine vaccination, but a minor illness is not. Breastfeeding and immunosuppression are not contraindications to vaccination. Studies of vaccination with MPSV4 during pregnancy have not documented adverse effects among either pregnant women or newborns. No data are available on the safety of MCV4 during pregnancy. However, pregnancy is not considered to be a contraindication to either MPSV4 or MCV4.

Meningococcal Vaccines
Contraindications and Precautions

- Severe allergic reaction to vaccine component or following a prior dose of vaccine
- Moderate or severe acute illness

Adverse Reactions Following Vaccination

Meningococcal Polysaccharide Vaccine

Adverse reactions to MPSV4 are generally mild. The most frequent are local reactions, such as pain and redness at the injection site. These reactions last for 1 or 2 days, and occur in up to 48% of recipients. Fever (100°–103°F) within 7 days of vaccination is reported for up to 3% of recipients. Systemic reactions, such as headache and malaise, within 7 days of vaccination are reported for up to 60% of recipients. Fewer than 3% of recipients reported these systemic reactions as severe.

Meningococcal Vaccines
Adverse Reactions

	MCV4	MPSV4
• Local reactions for 1-2 days	4%-48%	11%-59%
• Fever ≥100°F	3%	5%
• Systemic reactions (headache, malaise fatigue)	3%-60%	4%-62%

Meningococcal Conjugate Vaccine

Reported adverse reactions following MCV4 are similar to those reported after MPSV4. The most frequent are local reactions, which are reported in up to 59% of recipients. Fever (100°–103°F) within 7 days of vaccination is reported for up to 5% of recipients. Systemic reactions, such as headache and malaise are reported in up to 60% of recipients with 7 days of vaccination. Less than 3% of recipients reported these systemic reactions as severe.

As of December 31, 2008 the Vaccine Adverse Event Reporting System (VAERS) received 33 confirmed case reports of Guillain-Barré syndrome (GBS) after receipt of MCV4.

Symptom onset occurred 2 to 33 days after vaccination. Data are not sufficient to determine at this time if MCV4 increases the risk of GBS in persons who receive the vaccine. GBS is a rare illness, and the expected background population rates of GBS are not precisely known. Because ongoing known risk for serious meningococcal disease exists, CDC recommends continuation of current vaccination strategies. Whether receipt of MCV4 vaccine might increase the risk for recurrence of GBS is unknown. Until this issue is clarified, persons with a history of GBS who are not in a high-risk group for invasive meningococcal disease should not receive MCV4.

All severe adverse events that occur after receipt of any vaccine should be reported to VAERS. For information on reporting, see the VAERS website at http://www.vaers.hhs.gov.

Vaccine Storage and Handling

Both MPSV4 and MCV4 should be shipped in insulated containers to prevent exposure to freezing temperature. Vaccine should be stored at refrigerator temperature (35°–46° F, [2°–8° C]). The vaccines must not be exposed to freezing temperature, and any vaccine exposed to freezing temperature should not be used.

Single-dose vials of MPSV4 must be used within 30 minutes of reconstitution, and multidose vials must be discarded 10 days after reconstitution. MCV4 should not be drawn into a syringe until immediately before use.

Surveillance and Reporting of Meningococcal Disease

Invasive meningococcal disease is a reportable condition in most states. All healthcare personnel should report any case of invasive meningococcal disease to local and state health departments.

Antimicrobial Chemoprophylaxis

In the United States, the primary means for prevention of sporadic meningococcal disease is antimicrobial chemoprophylaxis of close contacts of infected persons. Close contacts include household members, child care center contacts, and anyone directly exposed to the patient's oral secretions (e.g., through kissing, mouth-to-mouth resuscitation, endotracheal intubation, or endotracheal tube management).

For travelers, antimicrobial chemoprophylaxis should be considered for any passenger who had direct contact with respiratory secretions from an index patient or for anyone seated directly next to an index patient on a prolonged flight (i.e., one lasting more than 8 hours). The attack rate for household contacts exposed to patients who have sporadic

meningococcal disease was estimated to be four cases per 1,000 persons exposed, which is 500–800 times greater than the rate for the total population. In the United Kingdom, the attack rate among healthcare personnel exposed to patients with meningococcal disease was determined to be 25 times higher than among the general population.

Because the rate of secondary disease for close contacts is highest immediately after onset of disease in the index patient, antimicrobial chemoprophylaxis should be administered as soon as possible, ideally less than 24 hours after identification of the index patient. Conversely, chemoprophylaxis administered more than 14 days after onset of illness in the index patient is probably of limited or no value. Oropharyngeal or nasopharyngeal cultures are not helpful in determining the need for chemoprophylaxis and might unnecessarily delay institution of this preventive measure.

Rifampin, ciprofloxacin, and ceftriaxone are 90%–95% effective in reducing nasopharyngeal carriage of *N. meningitidis* and are all acceptable antimicrobial agents for chemoprophylaxis. Systemic antimicrobial therapy for meningococcal disease with agents other than ceftriaxone or other third-generation cephalosporins might not reliably eradicate nasopharyngeal carriage of *N. meningitidis*. If other agents have been used for treatment, the index patient should receive chemoprophylactic antibiotics for eradication of nasopharyngeal carriage before being discharged from the hospital.

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Mumps

Mumps is an acute viral illness. Parotitis and orchitis were described by Hippocrates in the 5th century BCE. In 1934, Johnson and Goodpasture showed that mumps could be transmitted from infected patients to rhesus monkeys and demonstrated that mumps was caused by a filterable agent present in saliva. This agent was later shown to be a virus. Mumps was a frequent cause of outbreaks among military personnel in the prevaccine era, and was one of the most common causes of aseptic meningitis and sensorineural deafness in childhood. During World War I, only influenza and gonorrhea were more common causes of hospitalization among soldiers. A multistate mumps outbreak in 2006 resulted in more than 6,000 reported cases.

Mumps

- Acute viral illness
- Parotitis and orchitis described by Hippocrates in 5th century BCE
- Viral etiology described by Johnson and Goodpasture in 1934
- Frequent cause of outbreaks among military personnel in prevaccine era

Mumps Virus

Mumps virus is a paramyxovirus in the same group as parainfluenza and Newcastle disease virus. Parainfluenza and Newcastle disease viruses produce antibodies that cross-react with mumps virus. The virus has a single-stranded RNA genome.

The virus can be isolated or propagated in cultures of various human and monkey tissues and in embryonated eggs. It has been recovered from the saliva, cerebrospinal fluid, urine, blood, milk, and infected tissues of patients with mumps.

Mumps virus is rapidly inactivated by formalin, ether, chloroform, heat, and ultraviolet light.

Mumps Virus

- Paramyxovirus
- RNA virus
- One antigenic type
- Rapidly inactivated by chemical agents, heat, and ultraviolet light

Pathogenesis

The virus is acquired by respiratory droplets. It replicates in the nasopharynx and regional lymph nodes. After 12 to 25 days a viremia occurs, which lasts from 3 to 5 days. During the viremia, the virus spreads to multiple tissues, including the meninges, and glands such as the salivary, pancreas, testes, and ovaries. Inflammation in infected tissues leads to characteristic symptoms of parotitis and aseptic meningitis.

Mumps Pathogenesis

- Respiratory transmission of virus
- Replication in nasopharynx and regional lymph nodes
- Viremia 12-25 days after exposure with spread to tissues
- Multiple tissues infected during viremia

Clinical Features

The incubation period of mumps is 14 to 18 days (range, 14 to 25 days). The prodromal symptoms are nonspecific, and include myalgia, anorexia, malaise, headache, and low-grade fever.

Parotitis is the most common manifestation and occurs in 30% to 40% of infected persons. Parotitis may be unilateral or bilateral, and any combination of single or multiple salivary glands may be affected. Parotitis tends to occur within the first 2 days and may first be noted as earache and tenderness on palpation of the angle of the jaw. Symptoms tend to decrease after 1 week and usually resolve after 10 days.

Mumps Clinical Features

- Incubation period 14-18 days
- Nonspecific prodrome of myalgia, malaise, headache, low-grade fever
- Parotitis in 30%-40%
- Up to 20% of infections asymptomatic

As many as 20% of mumps infections are asymptomatic. An additional 40% to 50% may have only nonspecific or primarily respiratory symptoms.

Mumps Complications

CNS involvement	15% of clinical cases
Orchitis	20%-50% in post-pubertal males
Pancreatitis	2%-5%
Deafness	1/20,000
Death	Average 1 per year (1980 – 1999)

Complications

Central nervous system (CNS) involvement in the form of aseptic meningitis (inflammatory cells in cerebrospinal fluid) is common, occurring asymptomatically in 50% to 60% of patients. Symptomatic meningitis (headache, stiff neck) occurs in up to 15% of patients and resolves without sequelae in 3 to 10 days. Adults are at higher risk for this complication than are children, and boys are more commonly affected than girls (3:1 ratio). Parotitis may be absent in as many as 50% of such patients. Encephalitis is rare (less than 2 per 100,000 mumps cases).

Orchitis (testicular inflammation) is the most common complication in postpubertal males. It occurs in as many as 50% of postpubertal males, usually after parotitis, but it may precede it, begin simultaneously, or occur alone. It is bilateral in approximately 30% of affected males. There is usually abrupt onset of testicular swelling, tenderness, nausea, vomiting, and fever. Pain and swelling may subside in 1 week, but tenderness may last for weeks. Approximately 50% of patients with orchitis have some degree of testicular atrophy, but sterility is rare.

Oophoritis (ovarian inflammation) occurs in 5% of postpubertal females. It may mimic appendicitis. There is no relationship to impaired fertility.

Pancreatitis is infrequent, but occasionally occurs without parotitis; the hyperglycemia is transient and is reversible. Although single instances of diabetes mellitus have been reported, a causal relationship with mumps virus infection has yet to be conclusively demonstrated; many cases of temporal association have been described both in siblings and individuals, and outbreaks of diabetes have been reported a few months or years after outbreaks of mumps.

Deafness caused by mumps virus occurs in approximately 1 per 20,000 reported cases. Hearing loss is unilateral in approximately 80% of cases and may be associated with vestibular reactions. Onset is usually sudden and results in permanent hearing impairment.

Electrocardiogram changes compatible with myocarditis are seen in 3%–15% of patients with mumps, but symptomatic involvement is rare. Complete recovery is the rule, but deaths have been reported.

Other less common complications of mumps include arthralgia, arthritis, and nephritis. An average of one death from mumps per year was reported during 1980–1999.

Laboratory Diagnosis

The diagnosis of mumps is usually suspected based on clinical manifestations, in particular the presence of parotitis.

Mumps virus can be isolated from clinical specimens. The preferred sample for viral isolation is a swab from the parotid duct, or the duct of another affected salivary gland. Collection of viral samples from persons suspected of having mumps is strongly recommended. Mumps virus can also be detected by polymerase chain reaction (PCR).

Serology is the simplest method for confirming mumps virus infection and enzyme immunoassay (EIA), is the most commonly used test. EIA is widely available and is more sensitive than other serologic tests. It is available for both IgM and IgG. IgM antibodies usually become detectable during the first few days of illness and reach a peak about a week after onset. However, as with measles and rubella, mumps IgM may be transient or missing in persons who have had any doses of mumps-containing vaccine. Sera should be collected as soon as possible after symptom onset for IgM testing or as the acute-phase specimen for IgG seroconversion. Convalescent-phase sera should be collected 2 weeks later. A negative serologic test, especially in a vaccinated person, should not be used to rule out a mumps diagnosis because the tests are not sensitive enough to detect infection in all persons with clinical illness. In the absence of another diagnosis, a person meeting the clinical case definition should be reported as a mumps case.

Mumps Laboratory Diagnosis

- Isolation of mumps virus
- Detection of mumps antigen by PCR
- Serologic testing
  - —positive IgM antibody
  - —significant increase in IgG antibody between acute and convalescent specimens

Epidemiology

Occurrence

Mumps occurs worldwide.

Reservoir

Mumps is a human disease. Although persons with asymptomatic or nonclassical infection can transmit the virus, no carrier state is known to exist.

Transmission

Mumps is spread through airborne transmission or by direct contact with infected droplet nuclei or saliva.

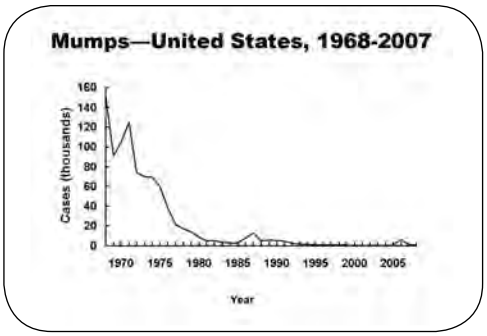
Temporal Pattern

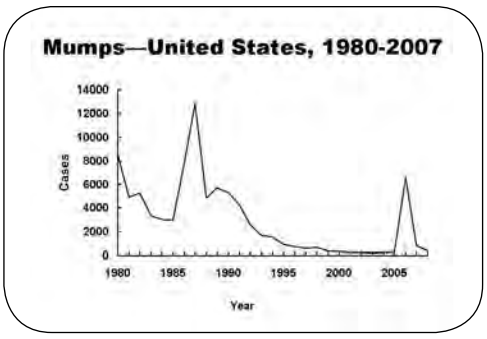
Mumps incidence peaks predominantly in late winter and spring, but the disease has been reported throughout the year.

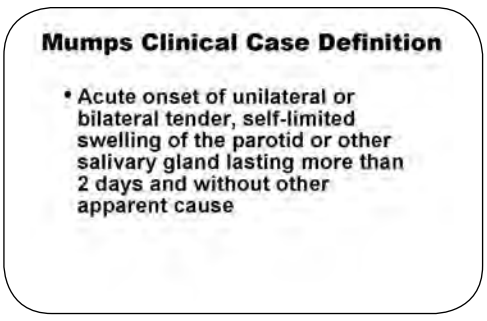
Mumps Epidemiology

• Reservoir	Human Asymptomatic infections may transmit
• Transmission	Respiratory drop nuclei
• Temporal pattern	Peak in late winter and spring
• Communicability	3 days before to 4 days after onset of active disease

Mumps







Communicability

Contagiousness is similar to that of influenza and rubella, but is less than that for measles or varicella. The infectious period is considered to be from 3 days before to the 4th day of active disease; virus has been isolated from saliva 7 days before to 9 days after onset of parotitis.

Secular Trends in the United States

Mumps became a nationally reportable disease in the United States in 1968. However, an estimated 212,000 cases occurred in the United States in 1964. Following vaccine licensure, reported mumps decreased rapidly. Approximately 3,000 cases were reported annually in 1983–1985 (1.3–1.55 cases per 100,000 population).

In 1986 and 1987, there was a relative resurgence of mumps, which peaked in 1987, when 12,848 cases were reported. The highest incidence of mumps during the resurgence was among older school-age and college-age youth (10–19 years of age), who were born before routine mumps vaccination was recommended. Mumps incidence in this period correlated with the absence of comprehensive state requirements for mumps immunization. Several mumps outbreaks among highly vaccinated school populations were reported, indicating that high coverage with a single dose of mumps vaccine did not always prevent disease transmission, probably because of vaccine failure.

Since 1989, the number of reported mumps cases has steadily declined, from 5,712 cases to a total of 258 cases in 2004. In 2006 a multistate mumps outbreak resulted in more than 6,000 reported cases. Eight states in the Midwest reported the majority of cases. The outbreak peaked in mid-April. The median age of persons reported with mumps was 22 years. Many cases occurred among college students, many of whom had received one or two doses of MMR vaccine.

Before vaccine licensure in 1967, and during the early years of vaccine use, most reported cases occurred in the 5–9-year age group; 90% of cases occurred among children 15 years of age and younger. In the late 1980s, there was a shift towards older children. Since 1990, persons age 15 years and older have accounted for 30% to 40% of cases per year (42% in 2002). Males and females are affected equally.

Eighty percent or more of adults in urban and suburban areas with or without a history of mumps have serologic evidence of immunity.

Case Definition

The clinical case definition of mumps is an acute onset of unilateral or bilateral tender, self-limited swelling of the

parotid or other salivary gland lasting more than 2 days and without other apparent cause.

Mumps Vaccine

Characteristics

Mumps virus was isolated in 1945, and an inactivated vaccine was developed in 1948. This vaccine produced only short-lasting immunity, and its use was discontinued in the mid-1970s. The currently used Jeryl Lynn strain of live attenuated mumps virus vaccine was licensed in December 1967.

Mumps vaccine is available combined with measles and rubella vaccines (as MMR), or combined with measles, rubella, and varicella vaccine as MMRV (ProQuad). The Advisory Committee on Immunization Practices (ACIP) recommends that MMR be used when any of the individual components is indicated. Use of single-antigen mumps vaccine is not recommended.

Mumps vaccine is prepared in chick embryo fibroblast tissue culture. MMR and MMRV are supplied as a lyophilized (freeze-dried) powder and are reconstituted with sterile, preservative-free water. The vaccine contains small amounts of human albumin, neomycin, sorbitol, and gelatin.

Mumps Vaccine

• Composition	Live virus (Jeryl Lynn strain)
• Efficacy	95% (Range, 90%-97%)
• Duration of Immunity	Lifelong
• Schedule	At least 1 dose

• Should be administered with measles and rubella (MMR) or with measles, rubella and varicella (MMRV)

Immunogenicity and Vaccine Efficacy

Mumps vaccine produces an inapparent, or mild, noncommunicable infection. More than 97% of recipients of a single dose develop measurable antibody. Seroconversion rates are similar for single antigen mumps vaccine, MMR, and MMRV. Postlicensure studies conducted in the United States during 1973–1989 determined that one dose of mumps or MMR vaccine was 75%–91% effective. A study from the United Kingdom documented vaccine effectiveness of 88% with two doses. The duration of vaccine-induced immunity is believed to be greater than 25 years, and is probably lifelong in most vaccine recipients.

Vaccination Schedule and Use

One dose of mumps-containing vaccine is routinely recommended for all preschool-age children 12 months of age and older and for persons born during or after 1957 not at high risk of mumps exposure. The first dose of mumps-containing vaccine should be given on or after the first birthday. Mumps-containing vaccine given before 12 months of age should not be counted as part of the series. Children vaccinated with mumps-containing vaccine before 12 months of age should be revaccinated with two doses of MMR vaccine, the first of which should be administered when the child is at least 12 months of age.

Mumps (MMR) Vaccine Indications

- One dose (as MMR) for preschool-age children 12 months of age and older and persons born during or after 1957 not at high risk of mumps exposure
- Second dose (as MMR) for school-age children and adults at high risk of mumps exposure (i.e., healthcare personnel, international travelers and students at post-high school educational institutions

Mumps

In 2006, ACIP recommended a second dose of mumps vaccine for school-age children and for adults at high risk of mumps exposure (i.e., healthcare personnel, international travelers, and students at post-high school educational institutions).The combined MMR vaccine is recommended for both doses to ensure immunity to all three viruses.

The second dose of MMR vaccine should be given routinely at age 4 through 6 years, before a child enters kindergarten or first grade. The recommended health visit at age 11 or 12 years can serve as a catch-up opportunity to verify vaccination status and administer MMR vaccine to those children who have not yet received two doses of MMR. The second dose of MMR may be administered as soon as 4 weeks (i.e., 28 days) after the first dose.

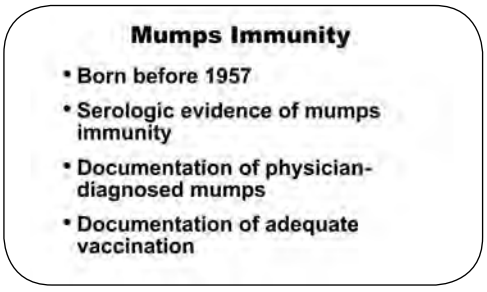
Only doses of vaccine with written documentation of the date of receipt should be accepted as valid. Self-reported doses or a parental report of vaccination is not considered adequate documentation. A clinician should not provide an immunization record for a patient unless that clinician has administered the vaccine or has seen a record that documents vaccination. Persons who lack adequate documentation of vaccination or other acceptable evidence of immunity should be vaccinated. Vaccination status and receipt of all vaccinations should be documented in the patient's permanent medical record and in a vaccination record held by the individual.

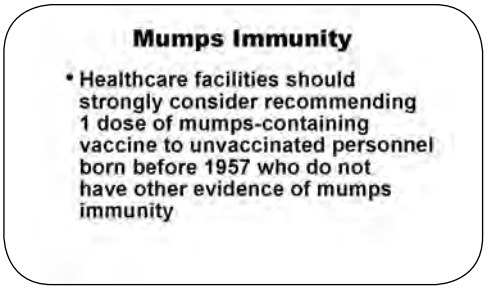
MMRV is approved by the Food and Drug Administration for children 12 months through 12 years of age (that is, until the 13th birthday). MMRV should not be administered to persons 13 years of age or older.

Mumps Immunity

Generally, persons can be considered immune to mumps if they were born before 1957, have serologic evidence of mumps immunity, have documentation of physician-diagnosed mumps, or have documentation of vaccination with at least one dose of live mumps vaccine on or after their first birthday. Demonstration of mumps IgG antibody by any commonly used serologic assay is acceptable evidence of mumps immunity. Persons who have an "equivocal" serologic test result should be considered susceptible to mumps.

Although persons born before 1957 can generally be considered to be immune to mumps, ACIP recommends that healthcare facilities should strongly consider recommending one dose of mumps-containing vaccine to unvaccinated healthcare personnel born before 1957 who do not have other evidence of mumps immunity, such as laboratory evidence of immunity.





Postexposure Prophylaxis

Neither mumps immune globulin nor immune globulin (IG) is effective postexposure prophylaxis. Vaccination after exposure is not harmful and may possibly avert later disease.

Contraindications and Precautions to Vaccination

Persons who have experienced a severe allergic reaction (anaphylaxis) to a vaccine component or following a prior close of mumps vaccine should generally not be vaccinated with MMR.

In the past, persons with a history of anaphylactic reactions following egg ingestion were considered to be at increased risk of serious reactions after receipt of measles- or mumps-containing vaccines, which are produced in chick embryo fibroblasts. However, data suggest that most anaphylactic reactions to measles- and mumps-containing vaccines are not associated with hypersensitivity to egg antigens but to other components of the vaccines (such as gelatin). The risk for serious allergic reactions such as anaphylaxis following receipt of these vaccines by egg-allergic persons is extremely low, and skin-testing with vaccine is not predictive of allergic reaction to vaccination. As a result, MMR may be administered to egg-allergic children without prior routine skin-testing or the use of special protocols.

MMR vaccine does not contain penicillin. A history of penicillin allergy is not a contraindication to MMR vaccination.

Pregnant women should not receive mumps vaccine, although the risk in this situation is theoretic. There is no evidence that mumps vaccine virus causes fetal damage. Pregnancy should be avoided for 4 weeks after vaccination with MMR vaccine.

Persons with immunodeficiency or immunosuppression resulting from leukemia, lymphoma, generalized malignancy, immune deficiency disease, or immunosuppressive therapy should not be vaccinated. However, treatment with low-dose (less than 2 mg/kg/day), alternate-day, topical, or aerosolized steroid preparations is not a contraindication to mumps vaccination. Persons whose immunosuppressive therapy with steroids has been discontinued for 1 month (3 months for chemotherapy) may be vaccinated. See Chapter 11, Measles, for additional details on vaccination of immunosuppressed persons, including those with human immunodeficiency virus infection.

Persons with moderate or severe acute illness should not be vaccinated until the illness has improved. Minor illness (e.g., otitis media, mild upper respiratory infections), concurrent

MMR Vaccine Contraindications and Precautions

- Severe allergic reaction to vaccine component or following a prior dose
- Pregnancy
- Immunosuppression
- Moderate or severe acute illness
- Recent blood product

Measles and Mumps Vaccines and Egg Allergy

- Measles and mumps viruses grown in chick embryo fibroblast culture
- Studies have demonstrated safety of MMR in egg allergic children
- Vaccinate without testing

antibiotic therapy, and exposure or recovery from other illnesses are not contraindications to mumps vaccination.

Receipt of antibody-containing blood products (e.g., immune globulin, whole blood or packed red blood cells, intravenous immune globulin) may interfere with seroconversion following mumps vaccination. Vaccine should be given 2 weeks before, or deferred for at least 3 months following, administration of an antibody-containing blood product. See Chapter 2, General Recommendations on Immunization, for details.

A family history of diabetes is not a contraindication for vaccination.

Adverse Reactions Following Vaccination

Mumps vaccine is very safe. Most adverse events reported following MMR vaccine (such as fever, rash, and joint symptoms) are attributable to the measles or rubella components. No adverse reactions were reported in large-scale field trials. Subsequently, parotitis and fever have been reported rarely. A few cases of orchitis (all suspect) also have been reported.

MMR Adverse Reactions

• Fever	5%-15%
• Rash	5%
• Joint symptoms	25%
• Thrombocytopenia	<1/30,000 doses
• Parotitis	rare
• Deafness	rare
• Encephalopathy	<1/1,000,000 doses

Rare cases of CNS dysfunction, including cases of deafness, within 2 months of mumps vaccination have been reported. The calculated incidence of CNS reactions is approximately one per 800,000 doses of Jeryl Lynn strain of mumps vaccine virus. The Institute of Medicine (1993) concluded that evidence is inadequate to accept or reject a causal relationship between the Jeryl Lynn strain of mumps vaccine and aseptic meningitis, encephalitis, sensorineural deafness, or orchitis.

Allergic reactions, including rash, pruritus, and purpura, have been temporally associated with vaccination, but these are transient and generally mild.

Vaccine Storage and Handling

MMR vaccine must be shipped with refrigerant to maintain a temperature of 50°F (10°C) or less at all times. Vaccine must be refrigerated immediately on arrival and protected from light at all times. The vaccine must be stored at refrigerator temperature (35°–46°F [2°–8°C]), but may be frozen. Diluent may be stored at refrigerator temperature or at room temperature. MMRV must be shipped to maintain a temperature of -4°F (-20°C) or less at all times. It must be stored at an average temperature of 5°F (-15°C) or less at all times.

After reconstitution, MMR vaccines must be stored at refrigerator temperature and protected from light. Reconstituted vaccine should be used immediately. If reconstituted vaccine

is not used within 8 hours, it must be discarded. MMRV must be administered within 30 minutes of reconstitution.

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Mumps

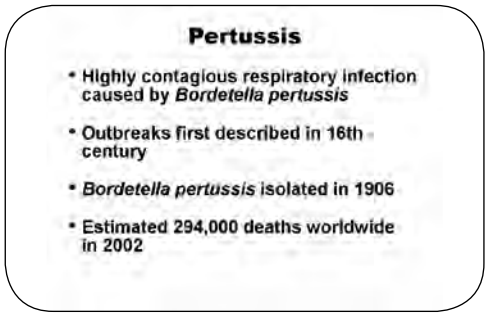
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Pertussis

Pertussis, or whooping cough, is an acute infectious disease caused by the bacterium *Bordetella pertussis*. Outbreaks of pertussis were first described in the 16th century, and the organism was first isolated in 1906.

In the 20th century, pertussis was one of the most common childhood diseases and a major cause of childhood mortality in the United States. Before the availability of pertussis vaccine in the 1940s, more than 200,000 cases of pertussis were reported annually. Since widespread use of the vaccine began, incidence has decreased more than 80% compared with the prevaccine era.

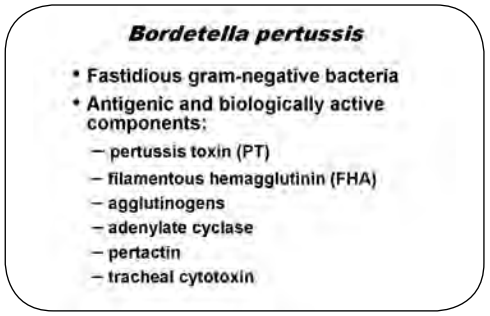
Pertussis remains a major health problem among children in developing countries, with 294,000 deaths resulting from the disease in 2002 (World Health Organization estimate).



Bordetella pertussis

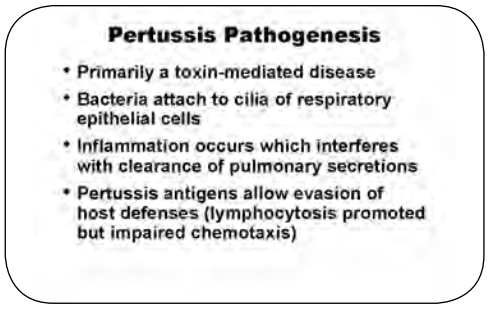
B. pertussis is a small, aerobic gram-negative rod. It is fastidious and requires special media for isolation (see Laboratory Diagnosis).

B. pertussis produces multiple antigenic and biologically active products, including pertussis toxin, filamentous hemagglutinin, agglutinogens, adenylate cyclase, pertactin, and tracheal cytotoxin. These products are responsible for the clinical features of pertussis disease, and an immune response to one or more produces immunity following infection. Immunity following *B. pertussis* infection does not appear to be permanent.



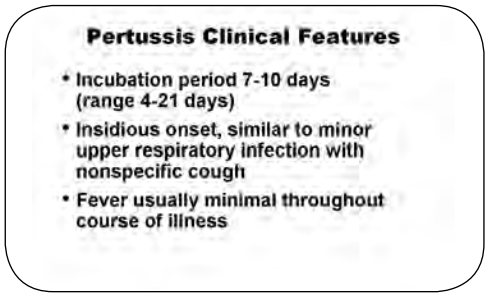
Pathogenesis

Pertussis is primarily a toxin-mediated disease. The bacteria attach to the cilia of the respiratory epithelial cells, produce toxins that paralyze the cilia, and cause inflammation of the respiratory tract, which interferes with the clearing of pulmonary secretions. Pertussis antigens appear to allow the organism to evade host defenses, in that lymphocytosis is promoted but chemotaxis is impaired. Until recently it was thought that *B. pertussis* did not invade the tissues. However, recent studies have shown the bacteria to be present in alveolar macrophages.



Clinical Features

The incubation period of pertussis is commonly 7–10 days, with a range of 4–21 days, and rarely may be as long as 42 days. The clinical course of the illness is divided into three stages.



Pertussis Clinical Features

• Catarrhal stage	1-2 weeks
• Paroxysmal cough stage	1-6 weeks
• Convalescence	Weeks to months

Pertussis Among Adolescents and Adults

- Disease often milder than in infants and children
- Infection may be asymptomatic, or may present as classic pertussis
- Persons with mild disease may transmit the infection
- Older persons often source of infection for children

The first stage, the catarrhal stage, is characterized by the insidious onset of coryza (runny nose), sneezing, low-grade fever, and a mild, occasional cough, similar to the common cold. The cough gradually becomes more severe, and after 1–2 weeks, the second, or paroxysmal stage, begins. Fever is generally minimal throughout the course of the illness.

It is during the paroxysmal stage that the diagnosis of pertussis is usually suspected. Characteristically, the patient has bursts, or paroxysms, of numerous, rapid coughs, apparently due to difficulty expelling thick mucus from the tracheobronchial tree. At the end of the paroxysm, a long inspiratory effort is usually accompanied by a characteristic high-pitched whoop. During such an attack, the patient may become cyanotic (turn blue). Children and young infants, especially, appear very ill and distressed. Vomiting and exhaustion commonly follow the episode. The person does not appear to be ill between attacks.

Paroxysmal attacks occur more frequently at night, with an average of 15 attacks per 24 hours. During the first 1 or 2 weeks of this stage, the attacks increase in frequency, remain at the same level for 2 to 3 weeks, and then gradually decrease. The paroxysmal stage usually lasts 1 to 6 weeks but may persist for up to 10 weeks. Infants younger than 6 months of age may not have the strength to have a whoop, but they do have paroxysms of coughing.

In the convalescent stage, recovery is gradual. The cough becomes less paroxysmal and disappears in 2 to 3 weeks. However, paroxysms often recur with subsequent respiratory infections for many months after the onset of pertussis.

Adolescents and adults and children partially protected by the vaccine may become infected with *B. pertussis* but may have milder disease than infants and young children. Pertussis infection in these persons may be asymptomatic, or present as illness ranging from a mild cough illness to classic pertussis with persistent cough (i.e., lasting more than 7 days). Inspiratory whoop is not common.

Even though the disease may be milder in older persons, those who are infected may transmit the disease to other susceptible persons, including unimmunized or incompletely immunized infants. Older persons are often found to have the first case in a household with multiple pertussis cases, and are often the source of infection for children.

Pertussis Complications*

Condition	Percent reported
Pneumonia	5.2
Seizures	0.8
Encephalopathy	0.1
Hospitalization	20
Death	0.2

*Cases reported to CDC 1997-2000 (N=28,187)

Complications

The most common complication, and the cause of most pertussis-related deaths, is secondary bacterial pneumonia. Young infants are at highest risk for acquiring pertussis-associated complications. Data from 1997–2000 indicate that

pneumonia occurred in 5.2% of all reported pertussis cases, and among 11.8% of infants younger than 6 months of age.

Neurologic complications such as seizures and encephalopathy (a diffuse disorder of the brain) may occur as a result of hypoxia (reduction of oxygen supply) from coughing, or possibly from toxin. Neurologic complications of pertussis are more common among infants. Other less serious complications of pertussis include otitis media, anorexia, and dehydration. Complications resulting from pressure effects of severe paroxysms include pneumothorax, epistaxis, subdural hematomas, hernias, and rectal prolapse.

In 2004 through 2006 a total of 82 deaths from pertussis were reported to the CDC. Children 3 months of age or younger accounted for 69 (84%) of these deaths.

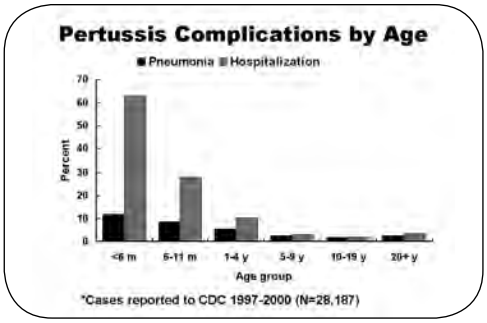
Adolescents and adults may also develop complications of pertussis, such as difficulty sleeping, urinary incontinence, pneumonia, and rib fracture.

Laboratory Diagnosis

The diagnosis of pertussis is based on a characteristic clinical history (cough for more than 2 weeks with whoop, paroxysms, or posttussive vomiting) as well as a variety of laboratory tests (culture, polymerase chain reaction [PCR], direct fluorescent antibody [DFA] and serology).

Culture is considered the gold standard laboratory test and is the most specific of the laboratory tests for pertussis. However, fastidious growth requirements make *B. pertussis* difficult to culture. The yield of culture can be affected by specimen collection, transportation, and isolation techniques. Specimens from the posterior nasopharynx, not the throat, should be obtained using Dacron® or calcium alginate (not cotton) swabs. Isolation rates are highest during the first 3 to 4 weeks of illness (catarrhal and early paroxysmal stages). Cultures are variably positive (30%–50%) and may take as long as 2 weeks, so results may be too late for clinical usefulness. Cultures are less likely to be positive if performed later in the course of illness (more than 2 weeks after cough onset) or on specimens from persons who have received antibiotics or have been vaccinated. Since adolescents and adults have often been coughing for several weeks before they seek medical attention, it is often too late for culture to be useful.

Because of the increased sensitivity and faster reporting of results of PCR, many laboratories are now using this method exclusively. PCR should be used in addition to, and not as a replacement for culture. No PCR product has been approved by the Food and Drug Administration (FDA), and there are no standardized protocols, reagents, or reporting



Pertussis Deaths in the United States, 2004-2006

	Age at onset <3 mos	>3 mos	Total
2004	24	3	27
2005	32	7	39
2006	13	3	16
Total	69	13	82
	(84%)	(16%)	

CDC, unpublished data, 2007

formats for pertussis PCR testing. Consequently, PCR assays vary widely among laboratories. Specificity can be poor, with high rates of false-positive results in some laboratories. Like culture, PCR is also affected by specimen collection. An inappropriately obtained nasopharyngeal swab will likely be negative by both culture and PCR. PCR is less affected by prior antibiotic therapy, since the organism does not need to be viable to be positive by PCR. Continued use of culture is essential for confirmation of PCR results.

DFA testing of nasopharyngeal specimens may be useful as a rapid screening test for pertussis. Use of the monoclonal DFA test has improved the specificity, but DFA still has a low sensitivity and should not be relied upon as a criterion for laboratory confirmation.

Serologic testing could be useful for adults and adolescents who present late in the course of their illness, when both culture and PCR are likely to be negative. However, there is no FDA-approved diagnostic test. The currently available serologic tests measure antibodies that could result from either infection or vaccination, so a positive serologic response simply means that the person has been exposed to pertussis by either recent or remote infection or by recent or remote vaccination. Since vaccination can induce both IgM and IgA antibodies (in addition to IgG antibodies), use of such serologic assays cannot differentiate infection from vaccine response. At this time, serologic test results should not be relied upon for case confirmation of pertussis infection.

An elevated white blood cell count with a lymphocytosis is usually present in classical disease of infants. The absolute lymphocyte count often reaches 20,000 or greater. However, there may be no lymphocytosis in some infants and children or in persons with mild or modified cases of pertussis. More information on the laboratory diagnosis of pertussis is available at http://www.cdc.gov/vaccines/pubs/surv-manual/default.pdf

Medical Management

The medical management of pertussis cases is primarily supportive, although antibiotics are of some value. Erythromycin is the drug of choice. This therapy eradicates the organism from secretions, thereby decreasing communicability and, if initiated early, may modify the course of the illness.

An antibiotic effective against pertussis (such as azithromycin, erythromycin or trimethoprim-sulfamethoxazole) should be administered to all close contacts of persons with pertussis, regardless of age and vaccination status. Revised treatment and postexposure prophylaxis recommendations were published in December 2005 (see reference list). All

close contacts younger than 7 years of age who have not completed the four-dose primary series should complete the series with the minimal intervals. (see table in Appendix A). Close contacts who are 4–6 years of age and who have not yet received the second booster dose (usually the fifth dose of DTaP) should be vaccinated. The administration of Tdap to persons 10 through 64 years of age who have been exposed to a person with pertussis is not contraindicated, but the efficacy of postexposure use of Tdap is unknown.

Epidemiology

Occurrence

Pertussis occurs worldwide.

Reservoir

Pertussis is a human disease. No animal or insect source or vector is known to exist. Adolescents and adults are an important reservoir for *B. pertussis* and are often the source of infection for infants.

Transmission

Transmission most commonly occurs by the respiratory route through contact with respiratory droplets, or by contact with airborne droplets of respiratory secretions. Transmission occurs less frequently by contact with freshly contaminated articles of an infected person.

Temporal Pattern

Pertussis has no distinct seasonal pattern, but it may increase in the summer and fall.

Communicability

Pertussis is highly communicable, as evidenced by secondary attack rates of 80% among susceptible household contacts. Persons with pertussis are most infectious during the catarrhal period and the first 2 weeks after cough onset (i.e., approximately 21 days).

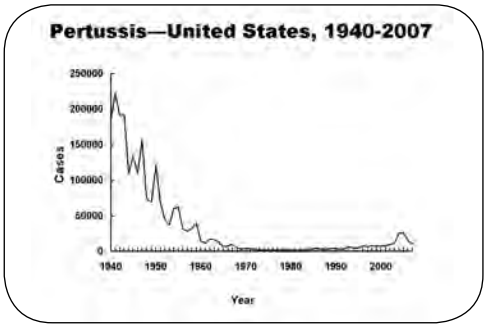
Secular Trends in the United States

Before the availability of vaccine, pertussis was a common cause of morbidity and mortality among children. During the 6-year period from 1940 through 1945, more than 1 million cases of pertussis were reported, an average of 175,000 cases per year (incidence of approximately 150 cases per 100,000 population).

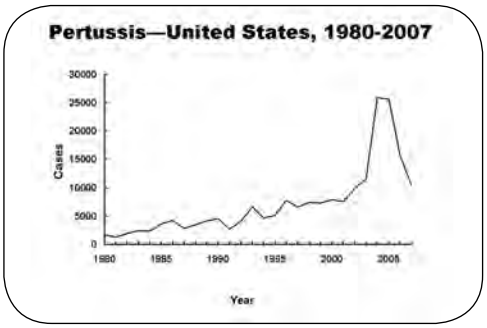
Following introduction of whole-cell pertussis vaccine in the 1940s, pertussis incidence gradually declined, reaching

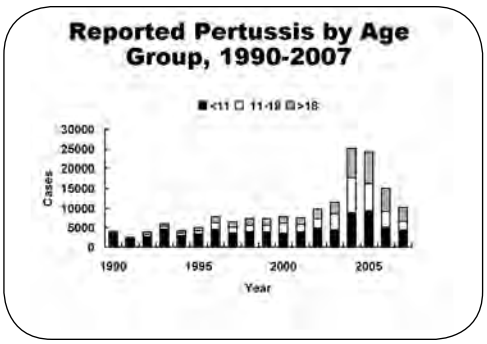
Pertussis Epidemiology

* Reservoir	Human Adolescents and adults
* Transmission	Respiratory droplets
* Communicability	Maximum in catarrhal stage Secondary attack rate up to 80%



Pertussis





15,000 reported cases in 1960 (approximately 8 per 100,000 population). By 1970, annual incidence was fewer than 5,000 cases per year, and during 1980–1990, an average of 2,900 cases per year were reported (approximately 1 per 100,000 population).

Pertussis incidence has been gradually increasing since the early 1980s. A total of 25,827 cases was reported in 2004, the largest number since 1959. The reasons for the increase are not clear.

During 2001–2003, the highest average annual pertussis incidence was among infants younger than 1 year of age (55.2 cases per 100,000 population), and particularly among children younger than 6 months of age (98.2 per 100,000 population). In 2002, 24% of all reported cases were in this age group. However, in recent years, adolescents (11–18 years of age) and adults (19 years and older) have accounted for an increasing proportion of cases. During 2001–2003, the annual incidence of pertussis among persons aged 10–19 years increased from 5.5 per 100,000 in 2001, to 6.7 in 2002, and 10.9 in 2003. In 2004 and 2005, approximately 60% of reported cases were among persons 11 years of age and older. Increased recognition and diagnosis of pertussis in older age groups probably contributed to this increase of reported cases among adolescents and adults.

Of the 10,650 children 3 months to 4 years of age with reported pertussis during 1990–1996 and known vaccination status, 54% were not age-appropriately vaccinated with DTaP.

Pertussis Surveillance

Pertussis cases are reported to CDC via two systems. States provide information about cases of pertussis, including demographic information, through the National Electronic Transmittal System for Surveillance. More detailed information is reported to CDC through the Supplementary Pertussis Surveillance System. Although many pertussis cases are not reported, the surveillance system is useful for monitoring epidemiologic trends. For instance, although the highest incidence of pertussis occurs in infancy, the age group at greatest risk for severe illness and complications, in recent years, the surveillance system has reflected an increase in the incidence of pertussis in all age groups, most notably among adolescents and adults.

Guidelines on pertussis surveillance and outbreak control are available at http://www.cdc.gov/vaccines/pubs/pertussis-guide/guide.htm.

Case Definition

The current case definition for pertussis was developed and adopted by the Council of State and Territorial Epidemiologists (CSTE) and CDC. It defines a clinical case of pertussis as an acute cough illness lasting at least 2 weeks with either paroxysms of coughing, inspiratory "whoop," or posttussive vomiting without other apparent cause (as reported by a health professional).

Case Classification

Probable—Meets the clinical case definition, but is not laboratory confirmed and is not epidemiologically linked to a laboratory-confirmed case.

Confirmed—A clinically compatible case that is laboratory confirmed or epidemiologically linked to a laboratory-confirmed case.

The clinical case definition above is appropriate for endemic or sporadic cases. In outbreak settings, including household exposures, a case can be defined as an acute cough illness lasting at least 2 weeks without other symptoms. See the pertussis chapter of the Manual for the Surveillance of Vaccine-Preventable Diseases (available at http://www.cdc.gov/vaccines/pubs/surv-manual/default.htm) for more information on case classification.

Pertussis Vaccines

Whole-Cell Pertussis Vaccine

Whole-cell pertussis vaccine is composed of a suspension of formalin-inactivated *B. pertussis* cells. It was developed in the 1930s and used widely in clinical practice by the mid-1940s.

Based on controlled efficacy trials conducted in the 1940s and on subsequent observational efficacy studies, a primary series of four doses of whole-cell DTP vaccine was 70%–90% effective in preventing serious pertussis disease. Protection decreased with time, resulting in little or no protection 5 to 10 years following the last dose. Local reactions such as redness, swelling, and pain at the injection site occurred following up to half of doses of whole-cell DTP vaccines. Fever and other mild systemic events were also common. Concerns about safety led to the development of more purified (acellular) pertussis vaccines that are associated with a lower frequency of adverse reactions. Whole-cell pertussis vaccines are no longer available in the United States but are still used in many other countries.

Whole-Cell Pertussis Vaccine

- Developed in mid-1930s and combined as DTP in mid-1940s
- 70%-90% efficacy after 3 doses
- Protection for 5-10 years
- Local adverse reactions common

Acellular Pertussis Vaccine

Characteristics

Acellular pertussis vaccines are subunit vaccines that contain purified, inactivated components of *B. pertussis* cells.

Several acellular pertussis vaccines have been developed for different age groups; these contain different pertussis components in varying concentrations. Acellular pertussis vaccines are available only as combinations with tetanus and diphtheria toxoids.

Pediatric Formulation (DTaP)

Three pediatric acellular pertussis vaccines are currently available for use in the United States. All three vaccines are combined with diphtheria and tetanus toxoids as DTaP and are approved for children 6 weeks through 6 years of age (to age 7 years). Infanrix (GlaxoSmithKline) contains three antigens, mostly pertussis toxin (PT) and FHA. Tripedia (sanofi pasteur) contains two components, FHA and PT, in equal amounts. Daptacel (sanofi pasteur) contains five components, PT, FHA, pertactin, and fimbriae types 2 and 3. None of the available DTaP vaccines contains thimerosal as a preservative, although Infanrix and Daptacel contain 2-phenoxyethanol as a preservative. Tripedia does not contain a preservative. All three vaccines are supplied in single-dose vials or syringes.

Pertussis-containing Vaccines

- DTaP (pediatric)
  - —approved for children 6 weeks through 6 years (to age 7 years)
- Tdap (adolescent and adult)
  - —approved for persons 10 through 64 years (Boostrix) and 11 through 64 years (Adacel)

Adolescent and Adult Formulation (Tdap)

Acellular pertussis–containing vaccines were first licensed for adolescents and adults in 2005. Two vaccines are currently available. Both vaccines are combined with tetanus toxoid and a reduced amount of diphtheria toxoid compared with pediatric DTaP (that is, similar quantities of tetanus and diphtheria toxoid to adult formulation Td). Boostrix (GlaxoSmithKline) is approved for persons 10 through 64 years of age, and contains three pertussis antigens (PT, FHA, and pertactin) in a reduced quantity compared with the GlaxoSmithKline pediatric formulation. The vaccine contains aluminum hydroxide as an adjuvant and does not contain a preservative. Adacel (sanofi pasteur) is approved for persons 11 through 64 years of age. It contains the same five pertussis components as Daptacel but with a reduced quantity of PT. Adacel contains aluminum phosphate as an adjuvant and does not contain a preservative. Both vaccines are supplied in single-dose vials or syringes.

Composition* of Acellular Pertussis Vaccines

Product	PT	FHA	PERT	FIM
Daptacel	10	5	3	5
Infanrix	25	25	8	--
Tripedia	23	23	--	--
Boostrix	8	8	2.5	--
Adacel	2.5	5	3	5

*mcg per dose

Immunogenicity and Vaccine Efficacy

DTaP

Since 1991, several studies conducted in Europe and Africa have evaluated the efficacy of DTaP vaccines administered to infants. These studies varied in type and number of vaccines, design, case definition, and laboratory method used to confirm the diagnosis of pertussis, so comparison among studies must b e made with caution. Point estimates of vaccine efficacy ranged from 80% to 85% for vaccines

DTaP Clinical Trials

Product	Location	VE (95% CI)
Daptacel	Sweden	85% (80-89)
Tripedia	Germany	80% (59-90)
Infanrix	Italy	84% (76-89)

currently licensed in the United States. Confidence intervals for vaccine efficacy overlap, suggesting that none of the vaccines is significantly more effective than the others. When studied, the acellular pertussis vaccine was significantly more effective than whole-cell DTP. Mild local and systemic adverse reactions and more serious adverse reactions (such as high fever, persistent crying, hypotonic hyporesponsive episodes, and seizures) occurred less frequently among infants vaccinated with acellular pertussis vaccines than among those vaccinated with whole-cell DTP.

Tdap

Adolescent and adult formulation Tdap vaccines were licensed on the basis of noninferiority of the serologic response to the various components compared with each company's pediatric DTaP formulation (Infanrix and Daptacel) among persons who had received pediatric DTaP or DTP in childhood. For both vaccines, the antibody response to a single dose of Tdap was similar to that following three doses of DTaP in infants. This type of study is known as "bridging." The new vaccines are assumed to have similar clinical efficacy as DTaP vaccine since a similar level of antibody to the components was achieved.

Vaccination Schedule and Use

DTaP

The primary series of DTaP vaccine consists of four doses, the first three doses given at 4- to 8-week intervals (minimum of 4 weeks), beginning at 6 weeks to 2 months of age. The fourth dose is given 6–12 months after the third to maintain adequate immunity for the ensuing preschool years. DTaP should be administered simultaneously with all other indicated vaccines.

Routine DTaP Primary Vaccination Schedule

Dose	Age	Minimum Interval
Primary 1	2 months	----
Primary 2	4 months	4 weeks
Primary 3	6 months	4 weeks
Primary 4	15-18 months	6 months

The fourth dose of all brands of DTaP is licensed, and recommended by ACIP, to be administered at 15–18 months of age (17–20 months for Daptacel). However, ACIP recommends that in certain circumstances the fourth dose be given earlier than 15 months of age. The fourth dose of DTaP may be given if the child is at least 12 months of age, and at least 6 months have elapsed since the third dose of pertussis vaccine was given, and, in the opinion of the immunization provider, the child is unlikely to return for an additional visit at 15–18 months of age. All three of these criteria should be met in order to administer the fourth dose of DTaP at 12–14 months of age.

DTaP Fourth Dose

- Recommended at 15-18 months*
- May be given earlier if:
  - child is 12 months of age, and
  - 6 months since DTaP3, and
  - unlikely to return at 15-18 months

*17-20 months for Daptacel

Children who received all four primary doses before the fourth birthday should receive a fifth (booster) dose of DTaP before entering school. This booster dose is not necessary (but may be given) if the fourth dose in the primary series

was given on or after the fourth birthday. The booster dose increases antibody levels and may decrease the risk of school-age children transmitting the disease to younger siblings who are not fully vaccinated.

For children who started the vaccination series with whole-cell DTP, DTaP should be substituted for any remaining doses of the pertussis series.

Interchangeability of Different Brands of DTaP Vaccine

- Series should be completed with same brand of vaccine if possible
- Limited data suggest that "mix and match" DTaP schedules do not adversely affect safety and immunogenicity
- Use different brand of DTaP if necessary

ACIP recommends that the series be completed with the same brand of DTaP vaccine if possible. However, limited data suggest that "mix and match" DTaP schedules do not adversely affect safety and immunogenicity. If the vaccine provider does not know or have available the type of DTaP vaccine previously administered to a child, any available DTaP vaccine should be used to continue or complete the vaccination series. Unavailability of the vaccine used for earlier doses is not a reason for missing the opportunity to administer a dose of acellular pertussis vaccine for which the child is eligible.

Interruption of the recommended schedule or delayed doses does not lead to a reduction in the level of immunity reached on completion of the primary series. There is no need to restart a series regardless of the time that has elapsed between doses.

Tdap

Tdap Vaccines

- Boostrix (GlaxoSmithKline)
  - — approved for persons 10 through 64 years of age
- Adacel (sanofi pasteur)
  - — approved for persons 11 through 64 years of age

Both Tdap vaccines are approved by the Food and Drug Administration for a single (booster) dose for persons who have completed the recommended childhood DTP/DTaP vaccination series. Boostrix is approved for persons 10 through 64 years of age; Adacel is approved for persons 11 through 64 years of age.

ACIP recommends that adolescents 11 or 12 years of age should receive a single dose of Tdap instead of Td. Adolescents 13 through 18 years who have not received Tdap should receive a single dose of Tdap as their catch-up booster instead of Td if they have completed the recommended childhood DTaP/DTP vaccination series, and have not yet received a Td booster.

Recommendations for Tdap Vaccination of Adolescents

- Adolescents 11 or 12 years of age should receive a single dose of Tdap instead of Td*
- Adolescents 13 through 18 years who have not received Tdap should receive a single dose of Tdap as their catch-up booster instead of Td*

*if the person has completed the recommended childhood DTaP/DTP vaccination series, and has not yet received a Td booster

MMWR 2006;55(RR-3):1-43.

A 5-year interval between Td and Tdap is encouraged to reduce the risk of local and systemic adverse reactions. However, ACIP did not define an absolute minimum interval between Td and Tdap. The interval between Td and Tdap may be shorter than 5 years if protection from pertussis needed. The decision whether to administer Tdap when less than 5 years has elapsed since the last dose of Td should be based on whether the benefit of pertussis immunity outweighs the risk of a local adverse reaction. An interval of less than 5 years can be considered in situations

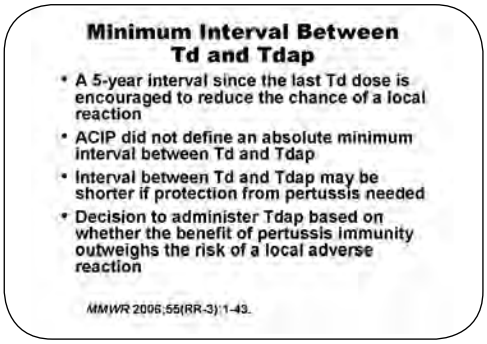
of increased risk of pertussis, such as during a pertussis outbreak, or if protection is needed because of household or other close contact with an infant younger than 12 months of age or a young child who has not been vaccinated against pertussis.

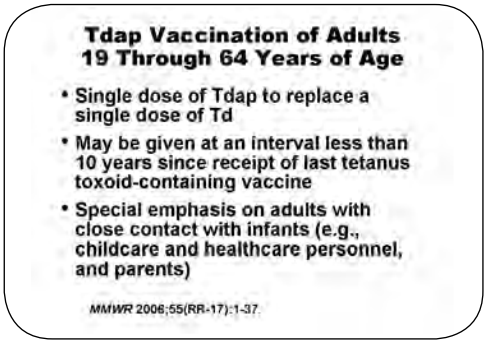
ACIP recommends that adults 19 through 64 years of age receive a single dose of Tdap to replace a single dose of Td for booster immunization against tetanus, diphtheria and pertussis. Tdap may be given at an interval less than 10 years since receipt of the last tetanus toxoid-containing vaccine to protect against pertussis. Special emphasis should be placed on Tdap vaccination of adults who have close contact with infants, such as childcare and healthcare personnel, and parents. Ideally, Tdap should be given at least 1 month before beginning close contact with the infant.

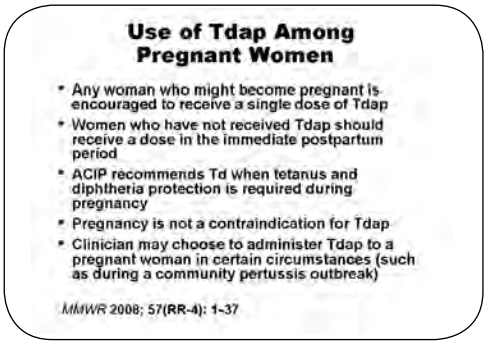
Any woman who might become pregnant is encouraged to receive a single dose of Tdap if she has not already received a dose. Women who have not received Tdap (including women who are breastfeeding) should receive a dose in the immediate postpartum period, before discharge from the hospital or birthing center, if 2 years or more have elapsed since the last Td. Shorter intervals since the last Td can be used if necessary. If Tdap cannot be administered before discharge, it should be given as soon as feasible. The dose of Tdap replaces the next routine dose of Td.

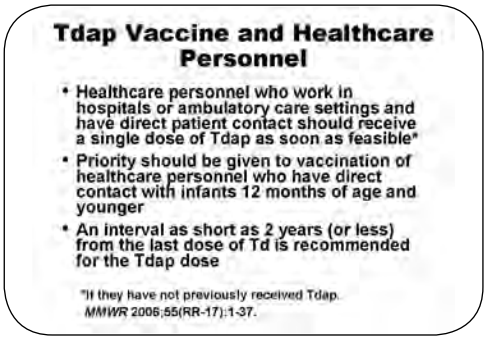
ACIP recommends Td when tetanus and diphtheria protection is required during pregnancy. However, pregnancy is not a contraindication for use of Tdap. A clinician may choose to administer Tdap to a pregnant woman in certain circumstances, such as during a community pertussis outbreak. When Td or Tdap is administered during pregnancy, the second or third trimester is preferred to avoid coincidental association of vaccination and spontaneous termination of a pregnancy, which is more common in the first trimester. Clinicians can choose to administer Tdap instead of Td to pregnant adolescents for routine or "catch-up" vaccination because the incidence of pertussis is high among adolescents. Others for whom Tdap might be considered during pregnancy are pregnant healthcare personnel and child care providers (to prevent transmission to infants younger than 12 months of age and to other vulnerable persons) and pregnant women employed in an institution or living in a community with increased pertussis activity.

Healthcare personnel who work in hospitals or ambulatory care settings and have direct patient contact should receive a single dose of Tdap as soon as feasible. Priority should be given to vaccination of healthcare personnel who have direct contact with infants 12 months of age and younger. An interval as short as 2 years (or less) from the last dose of Td is recommended for the Tdap dose.



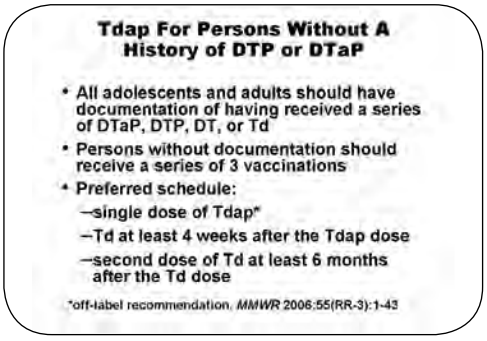






Tdap vaccine may be given at the same visit, or any time before or after any other vaccine.

Immunity following pertussis is not permanent. Persons with a history of pertussis should receive a single dose of Tdap if it is otherwise indicated.

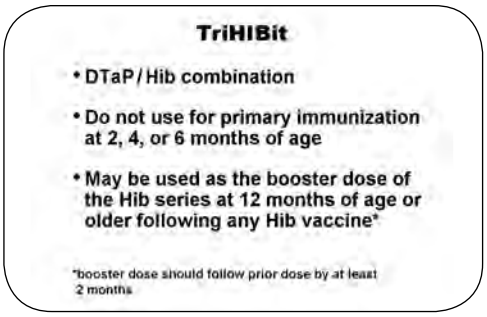


All adolescents and adults should have documentation of having received a primary series of at least three doses of tetanus and diphtheria toxoids during their lifetime. A person without such documentation should receive a series of three doses of tetanus- and diphtheria-containing vaccine. One of these doses, preferably the first, should be Tdap if the person is at least 10 years of age (the minimum age approved for one of the two available Tdap products). The remaining two doses should be adult formulation Td.

No pertussis vaccine is approved for children 7–9 years of age or for persons older than 64 years. ACIP does not recommend the use of Tdap in persons in these age groups.

Combination Vaccines Containing DTaP

TriHIBit



Two combination vaccines that contain DTap are currently licensed in the United States. TriHIBit (sanofi pasteur) contains DTaP and Hib (*Haemophilus influenzae* type b) vaccine. The vaccines are provided in separate vials, and the DTaP component (Tripedia) is used to reconstitute the Hib component (ActHIB). No other brand of DTaP and Hib vaccine may be used to produce this combination (e.g., Infanrix must not be substituted for Tripedia). In addition, when supplied as TriHIBit, the DTaP and Hib components have a single lot number. Providers should generally use only the DTaP and Hib supplied together as TriHIBit. However, it is acceptable to combine Tripedia and ActHIB that have been supplied separately (i.e., not packaged as TriHIBit). In this situation, the lot numbers of both vaccines should be recorded in the child's chart.

TriHIBit is not approved by the Food and Drug Administration for use as the primary series at 2, 4, or 6 months of age. It is approved only for the fourth dose of the DTaP and Hib series. If TriHIBit is administered as one or more doses of the primary series at 2, 4, or 6 months of age, the Hib doses should not be counted, and the child should be revaccinated as age-appropriate for Hib. The DTaP doses may be counted as valid and do not need to be repeated.

Although TriHIBit cannot be used in the primary series at

2, 4, or 6 months of age, it may be used as the booster (final) dose following a series of single-antigen Hib vaccine or combination hepatitis B–Hib vaccine (Comvax). TriHIBit can be used if the child is 12 months of age or older, has received at least one prior dose of Hib vaccine 2 or more months earlier, and TriHIBit will be the last dose in the Hib series. For example, TriHIBit can be used for the booster dose at 12–15 months of age in a child who has received Comvax or PedvaxHib at 2 and 4 months of age, or three prior doses of HibTiter or ActHib. TriHIBit can also be used at 15 through 59 months of age in a child who has received at least one prior dose of any Hib-containing vaccine. TriHIBit should not be used if the child has received no prior Hib doses.

Pediarix

In 2002, the FDA approved Pediarix (GlaxoSmithKline), the first pentavalent (5 component) combination vaccine licensed in the United States. Pediarix contains DTaP (Infanrix), hepatitis B (Engerix-B), and inactivated polio vaccines. In prelicensure studies, the proportion of children who developed a protective level of antibody and the titer of antibody were at least as high when the vaccine antigens were given together as Pediarix as when children received separate vaccines.

The minimum age for the first dose of Pediarix is 6 weeks, so it cannot be used for the birth dose of the hepatitis B series. Pediarix is approved for the first three doses of the DTaP and inactivated polio vaccine (IPV) series, which are usually given at about 2, 4, and 6 months of age; it is not approved for fourth or fifth (booster) doses of the DTaP or IPV series. However, Pediarix is approved for use through 6 years of age. A child who is behind schedule can receive Pediarix as long as it is given for doses 1, 2, or 3 of the series, and the child is younger than 7 years of age.

A dose of Pediarix inadvertently administered as the fourth or fifth dose of the DTaP or IPV series does not need to be repeated.

Pediarix may be used interchangeably with other pertussis-containing vaccines if necessary (although ACIP prefers the use of the same brand of DTaP for all doses of the series, if possible). It can be given at 2, 4, and 6 months to infants who received a birth dose of hepatitis B vaccine (total of four doses of hepatitis B vaccine). Although not labeled for this indication by FDA, Pediarix may be used in infants whose mothers are HBsAg positive or whose HBsAg status is not known.

Pediarix

- DTaP–Hep B–IPV combination
- Minimum age 6 weeks
- Approved for 3 doses at 2, 4 and 6 months
- Not approved for booster doses
- Licensed for children 6 weeks through 6 years of age

Pediarix

- May be used interchangeably with other pertussis-containing vaccines if necessary
- Can be given at 2, 4, and 6 months to infants who received a birth dose of hepatitis B vaccine (total of 4 doses)
- May be used in infants whose mothers are HBsAg positive or status is not known*

*off-label recommendation

Pentacel Vaccine

- Contains lyophilized Hib (ActHIB) vaccine that is reconstituted with a liquid DTaP-IPV solution
- Approved for doses 1 through 4 among children 6 weeks through 4 years of age
- The DTaP-IPV solution should not be used separately (i.e., only use to reconstitute the Hib component)

Pertussis Vaccine Use in Children with Underlying Neurologic Disorders

Underlying Condition	Recommendation
Prior seizure	Delay and assess*
Suspected neurologic disorder	Delay and assess*
Neurologic event between doses	Delay and assess*
Stable/resolved neurologic condition	Vaccinate

*vaccinate after treatment initiated and condition stabilized

Pertussis Vaccination of Children Who Have Recovered From Pertussis

- If documented disease, do not need additional doses of pediatric pertussis vaccine*
- Satisfactory documentation of disease:
  - —recovery of *B. pertussis* on culture, or
  - —typical symptoms and clinical course when epidemiologically linked to a culture-confirmed case

*Tdap is recommended when the child is age eligible

Pentacel

Pentacel is a combination vaccine that contains lyophilized Hib (ActHIB) vaccine that is reconstituted with a liquid DTaP-IPV solution. The vaccine was licensed by FDA in June 2008. Pentacel is licensed by FDA for doses 1 through 4 of the DTaP series among children 6 weeks through 4 years of age. The minimum intervals for Pentacel are determined by the DTaP component. The first three doses must be separated by at least 4 weeks. The fourth dose must be separated from the third by at least 6 calendar months, and not administered before 12 months of age. Pentacel should not be used for the fifth dose of the DTaP series, or for children 5 years or older regardless of the number of prior doses of the component vaccines.

The DTaP-IPV solution is licensed only for use as the diluent for the lyophilized Hib component and should not be used separately.

Other DTaP Issues

In certain circumstances, vaccination with DTaP vaccine should be delayed until a child with a known or suspected neurologic condition has been evaluated, treatment initiated, and the condition stabilized. These conditions include the presence of an evolving neurologic disorder (e.g., uncontrolled epilepsy, infantile spasms, and progressive encephalopathy), a history of seizures that has not been evaluated, or a neurologic event that occurs between doses of pertussis vaccine.

A family history of seizures or other neurologic diseases, or stable or resolved neurologic conditions (e.g., controlled idiopathic epilepsy, cerebral palsy, developmental delay) are not contraindications to pertussis vaccination. Acetaminophen or ibuprofen may be administered to children with such histories or conditions at the time of DTaP vaccination and for 24 hours thereafter to reduce the possibility of postvaccination fever, which could cause a febrile seizure.

Reducing the dose of whole-cell DTP or DTaP vaccine or giving the full dose in multiple smaller doses may result in an altered immune response and inadequate protection. Furthermore, there is no evidence that the chance of a significant vaccine reaction is likely to be reduced by this practice. The use of multiple reduced doses that together equal a full immunizing dose, or the use of smaller, divided doses is not endorsed or recommended. Any vaccination using less than the standard dose should not be counted, and the person should be revaccinated according to age.

Children who have recovered from documented pertussis do not need additional doses of pediatric pertussis vaccine. However, Tdap vaccine is recommended when the child becomes age eligible. Satisfactory documentation includes recovery of *B. pertussis* on culture or typical symptoms and clinical course when these are epidemiologically linked to a culture-confirmed case, as may occur during outbreaks. When such confirmation of diagnosis is lacking, vaccination should be completed because cough illness may be caused by other *Bordetella* species, other bacteria, or certain viruses.

Contraindications and Precautions to Vaccination

DTaP

Contraindications to further vaccination with DTaP are a severe allergic reaction (anaphylaxis) to a vaccine component or following prior dose of vaccine, and encephalopathy not due to another identifiable cause occurring within 7 days after vaccination.

Moderate or severe acute illness is a precaution to vaccination. Children with mild illness, such as otitis media or upper respiratory infection, should be vaccinated. Children for whom vaccination is deferred because of moderate or severe acute illness should be vaccinated when their condition improves.

Certain infrequent adverse reactions following DTaP vaccination are considered to be precautions for subsequent doses of pediatric pertussis vaccine. These adverse reactions are a temperature of 105°F (40.5°C) or higher within 48 hours that is not due to another identifiable cause; collapse or shock-like state (hypotonic hyporesponsive episode) within 48 hours; persistent, inconsolable crying lasting 3 hours or longer, occurring within 48 hours; and convulsions with or without fever occurring within 3 days.

There are circumstances (e.g., during a communitywide outbreak of pertussis) in which the benefit of vaccination outweighs the risk, even if one of the four precautionary adverse reactions occurred following a prior dose. In these circumstances, one or more additional doses of pertussis vaccine should be considered. DTaP should be used in these circumstances.

Tdap

Tdap is contraindicated for persons with a history of a severe allergic reaction to a vaccine component or following a prior dose of vaccine. Tdap is also contraindicated for persons with a history of encephalopathy not due to

DTaP Contraindications

- Severe allergic reaction to vaccine component or following a prior dose
- Encephalopathy not due to another identifiable cause occurring within 7 days after vaccination

DTaP Precautions*

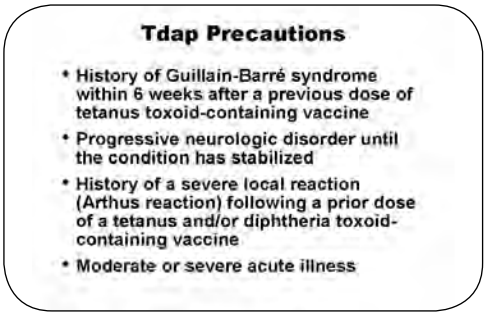
- Moderate or severe acute illness
- Temperature 105°F (40.5°C) or higher within 48 hours with no other identifiable cause
- Collapse or shock-like state (hypotonic hyporesponsive episode) within 48 hours
- Persistent, inconsolable crying lasting 3 hours or longer, occurring within 48 hours
- Convulsions with or without fever occurring within 3 days

*may consider use in outbreaks

Tdap Contraindications

- Severe allergic reaction to vaccine component or following a prior dose
- Encephalopathy not due to another identifiable cause occurring within 7 days after vaccination with a pertussis-containing vaccine

another identifiable cause occurring within 7 days after administration of a pertussis-containing vaccine.

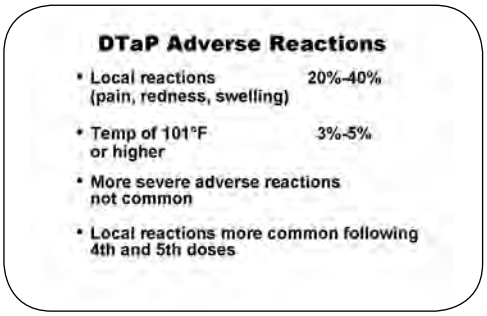


Precautions to Tdap include a history of Guillain-Barré syndrome within 6 weeks after a previous dose of tetanus toxoid-containing vaccine and a progressive neurologic disorder (such as uncontrolled epilepsy or progressive encephalopathy) until the condition has stabilized. Persons with a history of a severe local reaction (Arthus reaction) following a prior dose of a tetanus and/or diphtheria toxoid-containing vaccine should generally not receive Tdap or Td vaccination until at least 10 years have elapsed after the last Td-containing vaccine. Moderate or severe acute illness is a precaution to vaccination. Persons for whom vaccination is deferred because of moderate or severe acute illness should be vaccinated when their condition improves.

As noted above, certain conditions following DTaP vaccine, such as temperature of 105°F or higher, collapse or shock-like state, persistent crying, or convulsions with or without fever are a precaution to subsequent doses of DTaP. However, occurrence of one of these adverse reactions following DTaP vaccine in childhood is not a contraindication or precaution to administration of Tdap to an adolescent or adult. A history of extensive limb swelling following DTaP is not a contra- indication to Tdap vaccination. A stable neurologic disorder (such as controlled seizures or cerebral palsy), pregnancy, breastfeeding, and immunosuppression are not contraindications or precautions to administration of Tdap.

Adverse Reactions Following Vaccination

DTaP



As with all injected vaccines, administration of DTaP may cause local reactions, such as pain, redness, or swelling. Local reactions have been reported in 20%–40% of children after the first three doses. Local reactions appear to be more frequent after the fourth and/or fifth doses. Mild systemic reactions such as drowsiness, fretfulness, and low-grade fever may also occur. Temperature of 101°F or higher is reported in 3%–5% of DTaP recipients. These reactions are self-limited and can be managed with symptomatic treatment with acetaminophen or ibuprofen. Moderate or severe systemic reactions (such as fever [105°F or higher], febrile seizures, persistent crying lasting 3 hours or longer, and hypotonic hyporesponsive episodes) have been reported after administration of DTaP but occur less frequently than among children who received whole-cell DTP. Rates of these less common reactions vary by symptom and vaccine but generally occur in fewer than 1 in 10,000 doses. See

the pertussis chapter in the textbook Vaccines (Plotkin and Orenstein, eds., 2008) for a comprehensive review of DTaP adverse event data.

Information on adverse reactions following a full series of DTaP is also limited. Available data suggest a substantial increase in the frequency and magnitude of local reactions after the fourth and fifth doses. For example, swelling at the site of injection occurred in 2% of patients after the first dose of Tripedia, and in 29% following the fourth dose. Increases in the frequency of fever after the fourth dose have also been reported, although the increased frequencies of other systemic reactions (e.g., fretfulness, drowsiness, or decreased appetite) have not been observed. Further details on this issue can be found in a supplemental ACIP statement published in 2000 (*MMWR* 2000;49(No RR-13):1–8).

Adverse Reactions Following the 4th and 5th DTaP Dose

- Local adverse reactions and fever increased with 4th and 5th doses of DTaP
- Reports of swelling of entire limb
- Extensive swelling after 4th dose NOT a contraindication to 5th dose

Swelling involving the entire thigh or upper arm has been reported after booster doses of certain acellular pertussis vaccines. The limb swelling may be accompanied by erythema, pain and fever. Although the swelling may interfere with walking, most children have no limitation of activity. The pathogenesis and frequency of substantial local reactions and limb swelling are not known, but these conditions appear to be self-limited and resolve without sequelae.

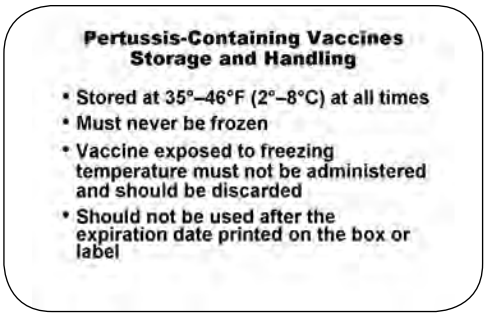
ACIP recommends that a fifth dose of DTaP be administered before a child enters school. It is not known whether children who experience entire limb swelling after a fourth dose of DTaP are at increased risk for this reaction after the fifth dose. Because of the importance of this dose in protecting a child during school years, ACIP recommends that a history of extensive swelling after the fourth dose should not be considered a contraindication to receipt of a fifth dose at school entry. Parents should be informed of the increase in reactogenicity that has been reported following the fourth and fifth doses of DTaP.

Tdap

The safety of Tdap vaccines was evaluated as part of prelicensure studies. The most common adverse reaction following both brands of Tdap vaccine is a local reaction, such as pain (66%), redness (25%) or swelling (21%) at the site of injection. Temperature of 100.4°F or higher was reported by 1.4% of Tdap recipients and 1.1% of Td recipients. Tdap recipients also reported a variety of nonspecific systemic events, such as headache, fatigue and gastrointestinal symptoms. Local reactions, fever, and nonspecific systemic symptoms occurred at approximately the same rate in recipients of Tdap and the comparison group that received Td without acellular pertussis vaccine. No serious adverse events have been attributed to Tdap.

Tdap Adverse Reactions

- Local reactions (pain, redness, swelling) 21%-66%
- Temp of 100.4°F or higher 1.4%
- Adverse reactions occur at approximately the same rate as Td alone (without acellular pertussis vaccine)



Vaccine Storage and Handling

DTaP, Td and Tdap vaccines should be stored at 35°–46°F (2°–8°C) at all times. The vaccines must never be frozen. Vaccine exposed to freezing temperature must not be administered and should be discarded. DTaP, Td and Tdap should not be used after the expiration date printed on the box or label.

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Pneumococcal Disease

Streptococcus pneumoniae causes an acute bacterial infection. The bacterium, also called pneumococcus, was first isolated by Pasteur in 1881 from the saliva of a patient with rabies. The association between the pneumococcus bacterium and lobar pneumonia was first described by Friedlander and Talamon in 1883, but pneumococcal pneumonia was confused with other types of pneumonia until the discovery of the Gram stain in 1884. From 1915 to 1945, the chemical structure and antigenicity of the pneumococcal capsular polysaccharide, its association with virulence, and the role of bacterial polysaccharides in human disease were explained. More than 80 serotypes of pneumococci had been described by 1940.

Efforts to develop effective pneumococcal vaccines began as early as 1911. However, with the advent of penicillin in the 1940s, interest in the vaccine declined, until it was observed that many patients still died despite antibiotic treatment. By the late 1960s, efforts were again being made to develop a polyvalent pneumococcal vaccine. The first pneumococcal vaccine was licensed in the United States in 1977. The first conjugate pneumococcal vaccine was licensed in 2000.

Pneumococcal Disease

- *S. pneumoniae* first isolated by Pasteur in 1881
- Confused with other causes of pneumonia until discovery of Gram stain in 1884
- More than 80 serotypes described by 1940
- First U.S. vaccine in 1977

Streptococcus pneumoniae

Streptococcus pneumoniae bacteria are lancet-shaped, gram-positive, facultative anaerobic organisms. They are typically observed in pairs (diplococci) but may also occur singularly or in short chains. Some pneumococci are encapsulated, their surfaces composed of complex polysaccharides. Encapsulated organisms are pathogenic for humans and experimental animals, whereas organisms without capsular polysaccharides are not. Capsular polysaccharides are the primary basis for the pathogenicity of the organism. They are antigenic and form the basis for classifying pneumococci by serotypes. Ninety serotypes have been identified, based on their reaction with type-specific antisera. Type-specific antibody to capsular polysaccharide is protective. These antibodies and complement interact to opsonize pneumococci, which facilitates phagocytosis and clearance of the organism. Antibodies to some pneumococcal capsular polysaccharides may cross-react with related types as well as with other bacteria, providing protection against additional serotypes.

Streptococcus pneumoniae

- Gram-positive bacteria
- 90 known serotypes
- Polysaccharide capsule important virulence factor
- Type-specific antibody is protective

Most *S. pneumoniae* serotypes have been shown to cause serious disease, but only a few serotypes produce the majority of pneumococcal infections. The 10 most common serotypes are estimated to account for about 62% of invasive disease worldwide. The ranking and serotype prevalence differ by patient age group and geographic area. In the United States, the seven most common serotypes isolated from blood or cerebrospinal fluid (CSF) of children younger

than 6 years of age account for 80% of infections. These seven serotypes account for only about 50% of isolates from older children and adults.

Pneumococci are common inhabitants of the respiratory tract and may be isolated from the nasopharynx of 5% to 70% of healthy adults. Rates of asymptomatic carriage vary with age, environment, and the presence of upper respiratory infections. Only 5%–10% of adults without children are carriers. In schools and orphanages, 27%–58% of students and residents may be carriers. On military installations, as many as 50%–60% of service personnel may be carriers. The duration of carriage varies and is generally longer in children than adults. In addition, the relationship of carriage to the development of natural immunity is poorly understood.

Clinical Features

The major clinical syndromes of pneumococcal disease are pneumonia, bacteremia, and meningitis. The immunologic mechanism that allows disease to occur in a carrier is not clearly understood. However, disease most often occurs when a predisposing condition exists, particularly pulmonary disease.

Pneumococcal Pneumonia Clinical Features

- Abrupt onset
- Fever
- Shaking chills
- Pleuritic chest pain
- Productive cough
- Dyspnea, tachypnea, hypoxia

Pneumococcal pneumonia is the most common clinical presentation of pneumococcal disease among adults, although pneumonia alone is not considered to be "invasive" disease. The incubation period of pneumococcal pneumonia is short, about 1 to 3 days. Symptoms generally include an abrupt onset of fever and chills or rigors. Typically there is a single rigor, and repeated shaking chills are uncommon. Other common symptoms include pleuritic chest pain, cough productive of mucopurulent, rusty sputum, dyspnea (shortness of breath), tachypnea (rapid breathing), hypoxia (poor oxygenation), tachycardia (rapid heart rate), malaise, and weakness. Nausea, vomiting, and headaches occur less frequently.

Pneumococcal Pneumonia

- Estimated 175,000 hospitalizations per year in the United States
- Up to 36% of adult community-acquired pneumonia and 50% of hospital-acquired pneumonia
- Common bacterial complication of influenza and measles
- Case-fatality rate 5%-7%, higher in elderly

As many as 175,000 hospitalizations from pneumococcal pneumonia are estimated to occur annually in the United States. Pneumococci account for up to 36% of adult community-acquired pneumonia and 50% of hospital-acquired pneumonia. Pneumonia is a common bacterial complication of influenza and measles. The case-fatality rate is 5%–7% and may be much higher among elderly persons. Complications of pneumococcal pneumonia include empyema (i.e., infection of the pleural space), pericarditis (inflammation of the sac surrounding the heart), and endobronchial obstruction, with atelectasis and lung abscess formation.

Pneumococcal Bacteremia

- More than 50,000 cases per year in the United States
- Rates higher among elderly and very young infants
- Case-fatality rate ~20%; up to 60% among the elderly

More than 50,000 cases of pneumococcal bacteremia occur each year. Bacteremia occurs in about 25%–30% of patients

with pneumococcal pneumonia. The overall case-fatality rate for bacteremia is about 20% but may be as high as 60% among elderly patients. Patients with asplenia who develop bacteremia may experience a fulminant clinical course.

Pneumococci cause 13%–19% of all cases of bacterial meningitis in the United States. An estimated 3,000 to 6,000 cases of pneumococcal meningitis occur each year. One-fourth of patients with pneumococcal meningitis also have pneumonia. The clinical symptoms, CSF profile and neurologic complications are similar to other forms of purulent bacterial meningitis. Symptoms may include headache, lethargy, vomiting, irritability, fever, nuchal rigidity, cranial nerve signs, seizures and coma. The case-fatality rate of pneumococcal meningitis is about 30% but may be as high as 80% among elderly persons. Neurologic sequelae are common among survivors. Persons with a cochlear implant appear to be at increased risk of pneumococcal meningitis.

Conditions that increase the risk of invasive pneumococcal disease include decreased immune function from disease or drugs, functional or anatomic asplenia, chronic heart, pulmonary including asthma, liver, or renal disease, smoking cigarettes, and cerebrospinal fluid, or CSF leak.

Pneumococcal Meningitis

- Estimated 3,000 - 6,000 cases per year in the United States
- Case-fatality rate ~30%, up to 80% in the elderly
- Neurologic sequelae common among survivors
- Increased risk after cochlear implant

Conditions That Increase Risk for Invasive Pneumococcal Disease

- Decreased immune function
- Asplenia (functional or anatomic)
- Chronic heart, pulmonary, liver or renal disease
- Cigarette smoking
- Cerebrospinal fluid (CSF) leak

Pneumococcal Disease in Children

Bacteremia without a known site of infection is the most common invasive clinical presentation of pneumococcal infection among children 2 years of age and younger, accounting for approximately 70% of invasive disease in this age group. Bacteremic pneumonia accounts for 12%–16% of invasive pneumococcal disease among children 2 years of age and younger. With the decline of invasive Hib disease, *S. pneumoniae* has become the leading cause of bacterial meningitis among children younger than 5 years of age in the United States. Before routine use of pneumococcal conjugate vaccine, children younger than 1 year had the highest rates of pneumococcal meningitis, approximately 10 cases per 100,000 population.

Pneumococci are a common cause of acute otitis media, and are detected in 28%–55% of middle ear aspirates. By age 12 months, more than 60% of children have had at least one episode of acute otitis media. Middle ear infections are the most frequent reasons for pediatric office visits in the United States, resulting in more than 20 million visits annually. Complications of pneumococcal otitis media may include mastoiditis and meningitis.

Before routine use of pneumococcal conjugate vaccine, the burden of pneumococcal disease among children younger than 5 years of age was significant. An estimated 17,000 cases of invasive disease occurred each year, of which 13,000

Pneumococcal Disease in Children

- Bacteremia without known site of infection most common clinical presentation
- *S. pneumoniae* leading cause of bacterial meningitis among children <5 years of age
- Common cause of acute otitis media

Burden of Pneumococcal Disease in Children*

Syndrome	Cases
Bacteremia	13,000
Meningitis	700
Death	200
Otitis media	5,000,000

*Prior to routine use of pneumococcal conjugate vaccine

were bacteremia without a known site of infection and about 700 were meningitis. An estimated 200 children died every year as a result of invasive pneumococcal disease. Although not considered invasive disease, an estimated 5 million cases of acute otitis media occured each year among children younger than 5 years of age.

Children at Increased Risk of Invasive Pneumococcal Disease

- Functional or anatomic asplenia, especially sickle cell disease
- HIV infection
- Alaska Native, African American, American Indian
- Child care attendance
- Cochlear implant

Children with functional or anatomic asplenia, particularly those with sickle cell disease, and children with human immunodeficiency virus (HIV) infection are at very high risk for invasive disease, with rates in some studies more than 50 times higher than those among children of the same age without these conditions (i.e., incidence rates of 5,000–9,000 per 100,000 population). Rates are also increased among children of certain racial and ethnic groups, in particular those of Alaska Native, African American, and certain American Indian groups (Arizona, New Mexico, and Navajo populations in Colorado and Utah). The reason for this increased risk by race and ethnicity is not known with certainty but was also noted for invasive *Haemophilus influenzae* infection (also an encapsulated bacterium). Attendance at a child care center has also been shown to increase the risk of invasive pneumococcal disease and acute otitis media 2–3-fold among children younger than 59 months of age. Children with a cochlear implant are at increased risk for pneumococcal meningitis.

Laboratory Diagnosis

A definitive diagnosis of infection with *S. pneumoniae* generally relies on isolation of the organism from blood or other normally sterile body sites. Tests are also available to detect capsular polysaccharide antigen in body fluids.

The appearance of lancet-shaped diplococci on Gram stain is suggestive of pneumococcal infection, but interpretation of stained sputum specimens may be difficult because of the presence of normal nasopharyngeal bacteria. The suggested criteria for obtaining a diagnosis of pneumococcal pneumonia using Gram stained sputnum includes more than 25 white blood cells and fewer than 10 epithelial cells per 100-power field, and a predominance of gram-positive diplococci.

The quellung reaction (capsular swelling; capsular precipitation reaction) is a test that provides rapid identification of pneumococci in clinical specimens, including spinal fluid, sputum, and exudates. The procedure involves mixing loopfuls of bacteria in suspension, pneumococcal antiserum, and methylene blue on the surface of a glass slide and examining under oil immersion. If the reaction is positive, the organism will be surrounded by a large capsule.

Several rapid tests for detection of pneumococcal polysaccharide antigen in CSF and other body fluids are available. These tests generally lack sufficient sensitivity or specificity to assist in the diagnosis of invasive pneumococcal disease.

Medical Management

Resistance to penicillin and other antibiotics is common. In some areas of the United States, up to 40% of invasive pneumococcal isolates are resistant to penicillin. Treatment will usually include a broad-spectrum cephalosporin, and often vancomycin, until results of antibiotic sensitivity testing are available.

Epidemiology

Occurrence

Pneumococcal disease occurs throughout the world.

Reservoir

S. pneumoniae is a human pathogen. The reservoir for pneumococci is presumably the nasopharynx of asymptomatic human carriers. There is no animal or insect vector.

Transmission

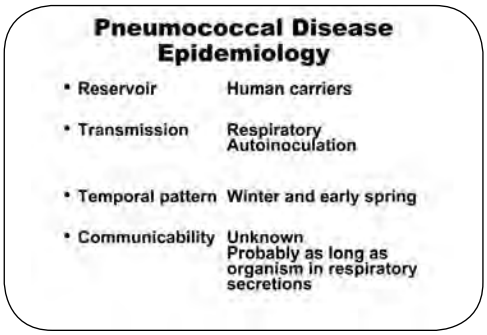
Transmission of *S. pneumoniae* occurs as the result of direct person-to-person contact via respiratory droplets and by autoinoculation in persons carrying the bacteria in their upper respiratory tract. The pneumococcal serotypes most often responsible for causing infection are those most frequently found in carriers. The spread of the organism within a family or household is influenced by such factors as crowding, season, and the presence of upper respiratory infections or pneumococcal disease such as pneumonia or otitis media. The spread of pneumococcal disease is usually associated with increased carriage rates. However, high carriage rates do not appear to increase the risk of disease transmission in households.

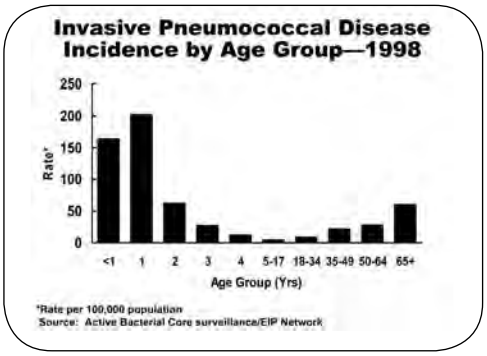
Temporal Pattern

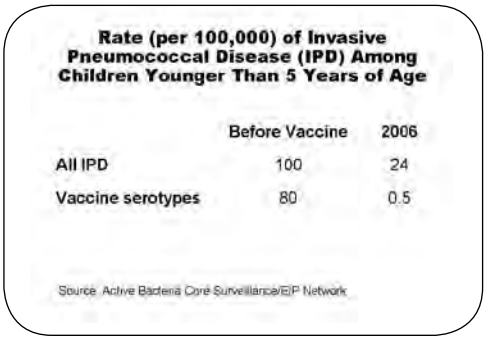
Pneumococcal infections are more common during the winter and in early spring when respiratory diseases are more prevalent.

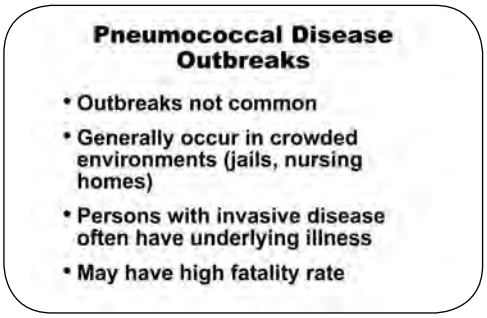
Communicability

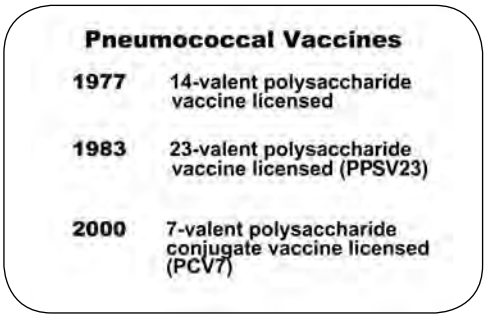
The period of communicability for pneumococcal disease is unknown, but presumably transmission can occur as long as the organism appears in respiratory secretions.











Secular Trends in the United States

Estimates of the incidence of pneumococcal disease have been made from a variety of population-based studies. More than 40,000 cases and more than 4,400 deaths from invasive pneumococcal disease (bacteremia and meningitis) are estimated to have occurred in the United States in 2007. More than half of these cases occurred in adults who had an indication for pneumococcal polysaccharide vaccine. In addition, there are thousands of cases of nonbacteremic pneumonia, and millions of cases of otitis media, which are considered noninvasive infections.

The overall incidence of invasive pneumococcal disease (bacteremia, meningitis, or other infection of a normally sterile site) in the United States in 1998–1999 was estimated to be approximately 24 cases per 100,000 population. However, incidence rates vary greatly by age group. The highest rates of invasive pneumococcal disease occur among young children, especially those younger than 2 years of age. In 1998, the rate of invasive disease in this age group was estimated to be 188 per 100,000 population; this age group accounted for 20% of all cases of invasive pneumococcal disease. Incidence was lowest among persons 5–17 years of age, and increased to 61 per 100,000 population among persons 65 years of age and older.

Data from the Active Bacterial Core surveillance (ABCs) system suggest that the use of pneumococcal conjugate vaccine is having an impact on the incidence of invasive disease among young children. Data from 2006 indicate that rates of invasive disease due to vaccine serotypes have declined more than 95% among children younger than 5 years of age, compared with 1998–1999 (prior to licensure of the vaccine).

Community-acquired pneumococcal pneumonia is usually a sporadic disease in carriers who have a breakdown in their pulmonary defense mechanisms. Outbreaks of pneumococcal pneumonia are not common. When outbreaks occur, they are usually in crowded environments, such as correctional facilities and nursing homes. During outbreaks, persons with invasive disease often have underlying illness and may have a high fatality rate.

Pneumococcal Vaccines

Characteristics

Pneumococcal Polysaccharide Vaccine

Pneumococcal polysaccharide vaccine is composed of purified preparations of pneumococcal capsular polysaccharide. The first polysaccharide pneumococcal vaccine was licensed in the United States in 1977. It contained purified capsular polysaccharide antigen from 14 different types of pneumococcal bacteria. In 1983, a 23-valent polysaccharide

vaccine (PPSV23) was licensed and replaced the 14-valent vaccine, which is no longer produced. PPSV23 contains polysaccharide antigen from 23 types of pneumococcal bacteria that cause 88% of bacteremic pneumococcal disease. In addition, cross-reactivity occurs for several capsular types that account for an additional 8% of bacteremic disease.

The polysaccharide vaccine currently available in the United States (Pneumovax 23, Merck) contains 25 mcg of each antigen per dose and contains 0.25% phenol as a preservative. The vaccine is available in a single-dose vial or syringe, and in a 5-dose vial. Pneumococcal vaccine is given by injection and may be administered either intramuscularly or subcutaneously.

Pneumococcal Polysaccharide Vaccine

- Purified capsular polysaccharide antigen from 23 types of pneumococcus
- Account for 88% of bacteremic pneumococcal disease
- Cross-react with types causing additional 8% of disease

Pneumococcal Conjugate Vaccine

The first pneumococcal conjugate vaccine (PCV7) was licensed in the United States in 2000. It includes purified capsular polysaccharide of seven serotypes of *S. pneumoniae* (4, 9V, 14, 19F, 23F, 18C, and 6B) conjugated to a nontoxic variant of diphtheria toxin known as CRM197. The serotypes included in PCV7 accounted for 86% of bacteremia, 83% of meningitis, and 65% of acute otitis media among children younger than 6 years of age in the United States during 1978–1994. Additional pneumococcal polysaccharide conjugate vaccines containing 9 and 11 serotypes of *S. pneumoniae* are being developed. The vaccine is administered intramuscularly. It does not contain thimerosal as a preservative, and is available only in single-dose vials.

Pneumococcal Conjugate Vaccine

- Pneumococcal polysaccharide conjugated to nontoxic diphtheria toxin (7 serotypes)
- Vaccine serotypes account for 86% of bacteremia and 83% of meningitis among children <6 years of age

Immunogenicity and Vaccine Efficacy

Pneumococcal Polysaccharide Vaccine

More than 80% of healthy adults who receive PPSV23 develop antibodies against the serotypes contained in the vaccine, usually within 2 to 3 weeks after vaccination. Older adults, and persons with some chronic illnesses or immunodeficiency may not respond as well, if at all. In children younger than 2 years of age, antibody response to most serotypes is generally poor. Elevated antibody levels persist for at least 5 years in healthy adults but decline more quickly in persons with certain underlying illnesses.

Pneumococcal Polysaccharide Vaccine

- Purified pneumococcal polysaccharide (23 types)
- Not effective in children <2 years
- 60%-70% against invasive disease
- Less effective in preventing pneumococcal pneumonia

PPSV23 vaccine efficacy studies have resulted in various estimates of clinical effectiveness. Overall, the vaccine is 60%–70% effective in preventing invasive disease. The vaccine may be less effective in preventing pneumococcal infection in some groups, particularly those with significant underlying illness. Although the vaccine may not be as effective in some persons, especially those who do not have normal resistance to infection, it is still recommended for such persons because they are at high risk of developing

severe disease. PPSV23 has not been demonstrated to provide protection against pneumococcal pneumonia. For this reason, providers should avoid referring to PPSV23 as "pneumonia vaccine."

Studies comparing patterns of pneumococcal carriage before and after PPSV23 vaccination have not shown clinically significant decreases in carrier rates among vaccinees. In addition, no change in the distribution of vaccine-type and non–vaccine-type organisms has been observed as the result of vaccination.

Pneumococcal Conjugate Vaccine

Pneumococcal Conjugate Vaccine

- Highly immunogenic in infants and young children, including those with high-risk medical conditions
- >90% effective against invasive disease
- Less effective against pneumonia and acute otitis media

After four doses of PCV7 vaccine, more than 90% of healthy infants develop antibody to all seven serotypes contained in the vaccine. PCV7 has been shown to be immunogenic in infants and children, including those with sickle cell disease and HIV infection. In a large clinical trial, PCV7 was shown to reduce invasive disease caused by vaccine serotypes by 97%, and reduce invasive disease caused by all serotypes, including serotypes not in the vaccine, by 89%. Efficacy against pneumonia varied depending on the specificity of the diagnosis. The vaccine reduced clinically diagnosed pneumonia by 11%, but reduced pneumonia confirmed by x-ray with consolidation of 2.5 or more centimeters by 73%. Children who received PCV7 had 7% fewer episodes of acute otitis media and underwent 20% fewer tympanostomy tube placements than did unvaccinated children. The duration of protection following PCV7 is currently not known. There is evidence that PCV7 reduces nasopharyngeal carriage of pneumococcal serotypes included in the vaccine.

Vaccination Schedule and Use

Pneumococcal Polysaccharide Vaccine

Pneumococcal Polysaccharide Vaccine Recommendations

- Adults 65 years of age or older
- Persons 2 years of age or older with
  - –chronic illness
  - –anatomic or functional asplenia
  - –immunocompromised (disease, chemotherapy, steroids)
  - –HIV infection
  - –environments or settings with increased risk
  - –cochlear implant

Pneumococcal polysaccharide vaccine should be administered routinely to all adults 65 years of age and older. The vaccine is also indicated for persons 2 years of age and older with a normal immune system who have a chronic illness, including cardiovascular disease, pulmonary disease, diabetes, alcoholism, cirrhosis, cerebrospinal fluid leak, or a cochlear implant.

Immunocompromised persons 2 years of age and older who are at increased risk of pneumococcal disease or its complications should also be vaccinated. This group includes persons with splenic dysfunction or absence (either from disease or surgical removal), Hodgkin disease, lymphoma, multiple myeloma, chronic renal failure, nephrotic syndrome (a type of kidney disease), or conditions such as organ transplantation associated with immunosuppression. Persons immunosuppressed from chemotherapy

or high-dose corticosteroid therapy (14 days or longer) should be vaccinated. Persons 2 years of age and older with asymptomatic or symptomatic HIV infection should be vaccinated. Pneumococcal vaccine should be considered for persons living in special environments or social settings with an identified increased risk of pneumococcal disease or its complications, such as certain Native American (i.e., Alaska Native, Navajo, and Apache) populations.

In 2008 ACIP added two new indications for pneumococcal polysaccharide vaccine for adults 19 years of age and older. These new indications are asthma and cigarette smoking. These groups were added because of evidence of an increased risk of invasive pneumococcal disease. Available data do NOT support asthma or cigarette smoking as indications for PPSV23 among persons younger than 19 years.

If elective splenectomy or cochlear implant is being considered, the vaccine should be given at least 2 weeks before the procedure. If vaccination prior to the procedure is not feasible, the vaccine should be given as soon as possible after surgery. Similarly, there should also be a 2-week interval between vaccination and initiation of cancer chemotherapy or other immunosuppressive therapy, if possible.

Providers should not withhold vaccination in the absence of an immunization record or complete record. The patient's verbal history may be used to determine vaccination status. Persons with uncertain or unknown vaccination status should be vaccinated.

The target groups for pneumococcal polysaccharide vaccine and influenza vaccine overlap. These vaccines should be given at the same time at different sites if indicated, although most recipients need only a single lifetime dose of PPSV23 (see Revaccination).

Pneumococcal Conjugate Vaccine

All children younger than 24 months of age and children age 24–59 months with a high-risk medical condition should be routinely vaccinated with PCV7. The primary series beginning in infancy consists of three doses routinely given at 2, 4, and 6 months of age. A fourth (booster) dose is recommended at 12–15 months of age. PCV7 should be administered at the same time as other routine childhood immunizations, using a separate syringe and injection site. For children vaccinated at younger than 12 months of age, the minimum interval between doses is 4 weeks. Doses given at 12 months of age and older should be separated by at least 8 weeks.

Unvaccinated children 7 months of age and older do not require a full series of four doses. The number of doses a

Pneumococcal Conjugate Vaccine

- Routine vaccination of children age <24 months and children 24-59 months with a high-risk medical condition
- Doses at 2, 4, 6, months of age, booster dose at 12-15 months of age
- Unvaccinated children ≥7 months of age require fewer doses

Pneumococcal Conjugate Vaccine

- Children aged 24-59 months at high risk and previously vaccinated with PPV23 should receive 2 doses of PCV7
- Children at high risk who previously received PCV7 should receive PPV23 at age ≥2 years

child needs to complete the series depends on the child's current age. Unvaccinated children aged 7 through 11 months should receive two doses of vaccine at least 4 weeks apart, followed by a booster dose at age 12 thorugh 15 months. Unvaccinated children aged 12 through 23 months should receive two doses of vaccine, at least 8 weeks apart. Previously unvaccinated healthy children 24 through 59 months of age should receive a single dose of PCV7. Unvaccinated children 24 through 59 months of age with sickle cell disease, asplenia, HIV infection, chronic illness, cochlear implant, or immunocompromising conditions should receive two doses of PCV7 separated by at least 8 weeks.

PCV7 is not routinely recommended for persons older than 59 months of age.

Few data are available on the use of PCV7 among children previously vaccinated with PPSV23. Children 24 through 59 months of age who have already received PPSV23 and who are at high risk of invasive pneumococcal disease (sickle cell disease, asplenia, cochlear implant, HIV infection or other immunocompromising conditions or chronic diseases) could benefit from the immunologic priming induced by PPSV23. ACIP recommends that these children receive two doses of PCV7 separated by at least 8 weeks. The first dose of PCV7 should be given no sooner than 2 months after PPSV23. Similarly, children 24 through 59 months of age who have already received one or more doses of PCV7 and who are at high risk of invasive pneumococcal disease will benefit from the additional serotypes included in PPSV23. Vaccination with PPSV23 should be considered for these high-risk children. PPSV23 should be given no sooner than 2 months after the last dose of PCV7. Routine administration of PPSV23 to healthy children 24 through 59 months of age is not recommended.

Revaccination

Pneumococcal Polysaccharide Vaccine Revaccination

- Routine revaccination of immunocompetent persons is not recommended
- Revaccination recommended for persons age ≥2 years at highest risk of serious pneumococcal infection
- Single revaccination dose ≥5 years after first dose

Pneumococcal Polysaccharide Vaccine

Following vaccination with PPSV23, antibody levels decline after 5–10 years and decrease more rapidly in some groups than others. However, the relationship between antibody titer and protection from invasive disease is not certain (i.e., higher antibody level does not necessarily mean better protection), so the ability to define the need for revaccination based only on serology is limited. In addition, currently available pneumococcal polysaccharide vaccines elicit a T-cell-independent response, and do not produce a sustained increase ("boost") in antibody titers. Available data do not indicate a substantial increase in protection in the majority of revaccinated persons.

Because of the lack of evidence of improved protection with multiple doses of pneumococcal vaccine, routine revaccination of immunocompetent persons previously vaccinated with 23-valent polysaccharide vaccine is not recommended. However, revaccination is recommended for persons 2 years of age and older who are at highest risk for serious pneumococcal infection and for those who are likely to have a rapid decline in pneumococcal antibody levels. Only one PPSV23 revaccination dose is recommended for high-risk persons. The second dose should be administered 5 or more years after the first dose. Revaccination 3 years after the previous dose may be considered for children at highest risk for severe pneumococcal infection who would be 10 years of age or less at the time of revaccination, including children who received PCV7.

Persons at highest risk include all persons 2 years of age and older with functional or anatomic asplenia (e.g., from sickle cell disease or splenectomy), HIV infection, leukemia, lymphoma, Hodgkin disease, multiple myeloma, generalized malignancy, chronic renal failure, nephrotic syndrome, or other conditions associated with immunosuppression (e.g., organ or bone marrow transplantation) and those receiving immunosuppressive chemotherapy, including long-term corticosteroids. Persons aged 65 years and older should be administered a second dose of pneumococcal vaccine if they received the vaccine more than 5 years previously, and were younger than 65 years of age at the time of the first dose.

Pneumococcal Polysaccharide Vaccine Candidates for Revaccination

- Persons ≥2 years of age with:
  - —functional or anatomic asplenia
  - —immunosuppression
  - —transplant
  - —chronic renal failure
  - —nephrotic syndrome
- Persons vaccinated at <65 years of age

Pneumococcal Conjugate Vaccine

Revaccination after an age-appropriate primary series with PCV7 is not currently recommended.

Contraindications and Precautions to Vaccination

For both pneumococcal polysaccharide and conjugate vaccines, a severe allergic reaction (anaphylaxis) to a vaccine component or following a prior dose is a contraindication to further doses of vaccine. Such allergic reactions are rare. Persons with moderate or severe acute illness should not be vaccinated until their condition improves. However, minor illnesses, such as upper respiratory infections, are not a contraindication to vaccination.

Pneumococcal Vaccines Contraindications and Precautions

- Severe allergic reaction to vaccine component or following prior dose of vaccine
- Moderate or severe acute illness

The safety of PPSV23 vaccine for pregnant women has not been studied, although no adverse consequences have been reported among newborns whose mothers were inadvertently vaccinated during pregnancy. Women who are at high risk of pneumococcal disease and who are candidates for pneumococcal vaccine should be vaccinated before pregnancy, if possible.

Pneumococcal Vaccines Adverse Reactions

• Local reactions	
—polysaccharide	30%-50%
—conjugate	10%-20%
• Fever, myalgia	
—polysaccharide	<1%
—conjugate	15%-24%
• Severe adverse reactions	rare

Adverse Reactions Following Vaccination

Pneumococcal Polysaccharide Vaccine

The most common adverse reactions following either pneumococcal polysaccharide or conjugate vaccine are local reactions. For PPSV23, 30%–50% of vaccinees report pain, swelling, or erythema at the site of injection. These reactions usually persist for less than 48 hours.

Local reactions are reported more frequently following a second dose of PPSV23 vaccine than following the first dose. Moderate systemic reactions (such as fever and myalgia) are not common (fewer than 1% of vaccinees), and more severe systemic adverse reactions are rare.

A transient increase in HIV replication has been reported following PPSV23 vaccine. No clinical or immunologic deterioration has been reported in these persons.

Pneumococcal Conjugate Vaccine

Local reactions following PCV7 occur in 10%–20% of recipients. Fewer than 3% of local reactions are considered to be severe (e.g., tenderness that interferes with limb movement). Local reactions are more common with the fourth dose than with the first three doses. In clinical trials of pneumococcal conjugate vaccine, fever (higher than 100.4°F [38°C]) within 48 hours of any dose of the primary series was reported for 15%–24% of children. However, in these studies, whole-cell pertussis vaccine was administered simultaneously with each dose, and some or most of the reported febrile episodes may be attributable to the DTP. In one study, acellular pertussis vaccine (DTaP) was given at the same visit as the booster dose of PCV7. In this study, 11% of recipients had a temperature higher than 102.2°F (39°C). No severe adverse events attributable to PCV7 have been reported.

Vaccine Storage and Handling

Pneumococcal polysaccharide vaccine should be shipped in an insulated container with coolant packs. Although pneumococcal polysaccharide vaccine can tolerate room temperature for a few days, CDC recommends that the vaccine be stored at refrigerator temperature (35°–46°F [2°–8°C]).

Pneumococcal conjugate vaccine should be stored at refrigerator temperature. Pneumococcal vaccines must not be frozen.

Opened multidose vials may be used until the expiration date printed on the package if they are not visibly contaminated.

Goals and Coverage Levels

The *Healthy People 2010* goal is to achieve at least 90% coverage for pneumococcal polysaccharide vaccine among persons 65 years of age and older. Data from the 2003 Behavioral Risk Factor Surveillance System (BRFSS, a population-based, random-digit-dialed telephone survey of the noninstitutionalized U.S. population 18 years of age and older) estimate that 64% of persons 65 years of age or older had ever received pneumococcal polysaccharide. Vaccination coverage levels were lower among persons 18–64 years of age with a chronic illness.

Pneumococcal Polysaccharide Vaccine Coverage

- Healthy People 2010 goal: 90% coverage for persons ≥65 years
- 2003 BRFSS: 64% of persons ≥65 years of age ever vaccinated
- Vaccination coverage levels were lower among persons 18-64 years of age with a chronic illness

Opportunities to vaccinate high-risk persons are missed both at the time of hospital discharge and during visits to clinicians' offices. Effective programs for vaccine delivery are needed, including offering the vaccine in hospitals at discharge and in clinicians' offices, nursing homes, and other long-term care facilities.

More than 65% of the persons who have been hospitalized with severe pneumococcal disease had been admitted to a hospital in the preceding 3–5 years, yet few had received pneumococcal vaccine. In addition, persons who frequently visit physicians and who have chronic conditions are more likely to be at high risk of pneumococcal infection than those who require infrequent visits. Screening and subsequent immunization of hospitalized persons found to be at high risk could have a significant impact on reducing complications and death associated with pneumococcal disease.

Pneumococcal Polysaccharide Vaccine Missed Opportunities

- >65% of patients with severe pneumococcal disease had been hospitalized within preceding 3-5 years yet few had received vaccine
- May be administered simultaneously with influenza vaccine

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Poliomyelitis

The words polio (grey) and myelon (marrow, indicating the spinal cord) are derived from the Greek. It is the effect of poliomyelitis virus on the spinal cord that leads to the classic manifestation of paralysis.

Records from antiquity mention crippling diseases compatible with poliomyelitis. Michael Underwood first described a debility of the lower extremities in children that was recognizable as poliomyelitis in England in 1789. The first outbreaks in Europe were reported in the early 19th century, and outbreaks were first reported in the United States in 1843. For the next hundred years, epidemics of polio were reported from developed countries in the Northern Hemisphere each summer and fall. These epidemics became increasingly severe, and the average age of persons affected rose. The increasingly older age of persons with primary infection increased both the disease severity and number of deaths from polio. Polio reached a peak in the United States in 1952, with more than 21,000 paralytic cases. However, following introduction of effective vaccines, polio incidence declined rapidly. The last case of wild-virus polio acquired in the United States was in 1979, and global polio eradication may be achieved within the next decade.

Poliomyelitis

- First described by Michael Underwood in 1789
- First outbreak described in U.S. in 1843
- More than 21,000 paralytic cases reported in the U.S. in 1952
- Global eradication within next decade

Poliovirus

Poliovirus is a member of the enterovirus subgroup, family Picornaviridae. Enteroviruses are transient inhabitants of the gastrointestinal tract, and are stable at acid pH. Picornaviruses are small, ether-insensitive viruses with an RNA genome.

There are three poliovirus serotypes (P1, P2, and P3). There is minimal heterotypic immunity between the three serotypes. That is, immunity to one serotype does not produce significant immunity to the other serotypes.

The poliovirus is rapidly inactivated by heat, formaldehyde, chlorine, and ultraviolet light.

Poliovirus

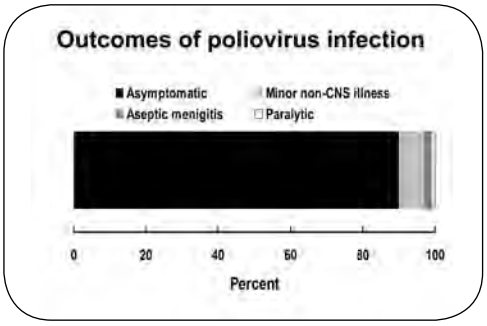
- Enterovirus (RNA)
- Three serotypes: 1, 2, 3
- Minimal heterotypic immunity between serotypes
- Rapidly inactivated by heat, formaldehyde, chlorine, ultraviolet light

Pathogenesis

The virus enters through the mouth, and primary multiplication of the virus occurs at the site of implantation in the pharynx and gastrointestinal tract. The virus is usually present in the throat and in the stool before the onset of illness. One week after onset there is less virus in the throat, but virus continues to be excreted in the stool for several weeks. The virus invades local lymphoid tissue, enters the bloodstream, and then may infect cells of the central nervous system. Replication of poliovirus in motor neurons of the anterior horn and brain stem results in cell destruction and causes the typical manifestations of poliomyelitis.

Poliomyelitis Pathogenesis

- Entry into mouth
- Replication in pharynx, GI tract, local lymphatics
- Hematologic spread to lymphatics and central nervous system
- Viral spread along nerve fibers
- Destruction of motor neurons



Clinical Features

The incubation period for poliomyelitis is commonly 6 to 20 days with a range of 3 to 35 days.

The response to poliovirus infection is highly variable and has been categorized on the basis of the severity of clinical presentation.

Up to 95% of all polio infections are inapparent or asymptomatic. Estimates of the ratio of inapparent to paralytic illness vary from 50:1 to 1,000:1 (usually 200:1). Infected persons without symptoms shed virus in the stool and are able to transmit the virus to others.

Approximately 4%–8% of polio infections consist of a minor, nonspecific illness without clinical or laboratory evidence of central nervous system invasion. This clinical presentation is known as abortive poliomyelitis, and is characterized by complete recovery in less than a week. Three syndromes observed with this form of poliovirus infection are upper respiratory tract infection (sore throat and fever), gastrointestinal disturbances (nausea, vomiting, abdominal pain, constipation or, rarely, diarrhea), and influenza-like illness. These syndromes are indistinguishable from other viral illnesses.

Nonparalytic aseptic meningitis (symptoms of stiffness of the neck, back, and/or legs), usually following several days after a prodrome similar to that of minor illness, occurs in 1%–2% of polio infections. Increased or abnormal sensations can also occur. Typically these symptoms will last from 2 to 10 days, followed by complete recovery.

Fewer than 1% of all polio infections result in flaccid paralysis. Paralytic symptoms generally begin 1 to 10 days after prodromal symptoms and progress for 2 to 3 days. Generally, no further paralysis occurs after the temperature returns to normal. The prodrome may be biphasic, especially in children, with initial minor symptoms separated by a 1- to 7-day period from more major symptoms. Additional prodromal signs and symptoms can include a loss of superficial reflexes, initially increased deep tendon reflexes and severe muscle aches and spasms in the limbs or back. The illness progresses to flaccid paralysis with diminished deep tendon reflexes, reaches a plateau without change for days to weeks, and is usually asymmetrical. Strength then begins to return. Patients do not experience sensory losses or changes in cognition.

Many persons with paralytic poliomyelitis recover completely and, in most, muscle function returns to some degree. Weakness or paralysis still present 12 months after onset is usually permanent.

Paralytic polio is classified into three types, depending on

the level of involvement. Spinal polio is most common, and during 1969–1979, accounted for 79% of paralytic cases. It is characterized by asymmetric paralysis that most often involves the legs. Bulbar polio leads to weakness of muscles innervated by cranial nerves and accounted for 2% of cases during this period. Bulbospinal polio, a combination of bulbar and spinal paralysis, accounted for 19% of cases.

The death-to-case ratio for paralytic polio is generally 2%–5% among children and up to 15%–30% for adults (depending on age). It increases to 25%–75% with bulbar involvement.

Laboratory Diagnosis

Viral Isolation

Poliovirus may be recovered from the stool or pharynx of a person with poliomyelitis. Isolation of virus from the cerebrospinal fluid (CSF) is diagnostic, but is rarely accomplished.

If poliovirus is isolated from a person with acute flaccid paralysis, it must be tested further, using oligonucleotide mapping (fingerprinting) or genomic sequencing, to determine if the virus is "wild type" (that is, the virus that causes polio disease) or vaccine type (virus that could derive from a vaccine strain).

Serology

Neutralizing antibodies appear early and may be at high levels by the time the patient is hospitalized; therefore, a fourfold rise in antibody titer may not be demonstrated.

Cerebrospinal Fluid

In poliovirus infection, the CSF usually contains an increased number of white blood cells (10–200 cells/mm3, primarily lymphocytes) and a mildly elevated protein (40–50 mg/100 mL).

Epidemiology

Occurrence

At one time poliovirus infection occurred throughout the world. Transmission of wild poliovirus was interrupted in the United States in 1979, or possibly earlier. A polio eradication program conducted by the Pan American Health Organization led to elimination of polio in the Western Hemisphere in 1991. The Global Polio Eradication Program has dramatically reduced poliovirus transmission throughout the world. In 2008, only 1,655 confirmed cases of polio were reported globally and polio was endemic in four countries.

Reservoir

Humans are the only known reservoir of poliovirus, which is transmitted most frequently by persons with inapparent infections. There is no asymptomatic carrier state except in immune deficient persons.

Transmission

Person-to-person spread of poliovirus via the fecal-oral route is the most important route of transmission, although the oral-oral route may account for some cases.

Temporal Pattern

Poliovirus infection typically peaks in the summer months in temperate climates. There is no seasonal pattern in tropical climates.

Communicability

Poliovirus is highly infectious, with seroconversion rates among susceptible household contacts of children nearly 100%, and greater than 90% among susceptible household contacts of adults. Persons infected with poliovirus are most infectious from 7 to 10 days before and after the onset of symptoms, but poliovirus may be present in the stool from 3 to 6 weeks.

Poliovirus Epidemiology

• Reservoir	Human
• Transmission	Fecal-oral Oral-oral possible
• Communicability	7 to 10 days before onset Virus present in stool 3 to 6 weeks

Secular Trends in the United States

Before the 18th century, polioviruses probably circulated widely. Initial infections with at least one type probably occurred in early infancy, when transplacentally acquired maternal antibodies were high. Exposure throughout life probably provided continual boosting of immunity, and paralytic infections were probably rare. (This view has been recently challenged based on data from lameness studies in developing countries.)

In the immediate prevaccine era, improved sanitation allowed less frequent exposure and increased the age of primary infection. Boosting of immunity from natural exposure became more infrequent and the number of susceptible persons accumulated, ultimately resulting in the occurrence of epidemics, with 13,000 to 20,000 paralytic cases reported annually.

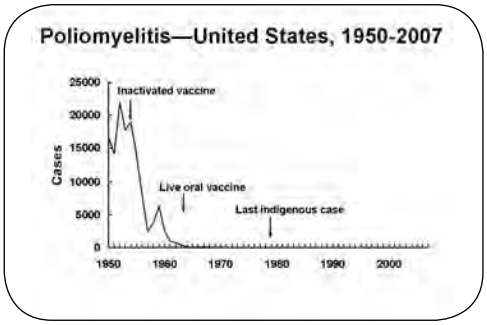
In the early vaccine era, the incidence dramatically decreased after the introduction of inactivated polio vaccine (IPV) in 1955. The decline continued following oral polio vaccine (OPV) introduction in 1961. In 1960, a total of 2,525 paralytic cases were reported, compared with 61 in 1965.

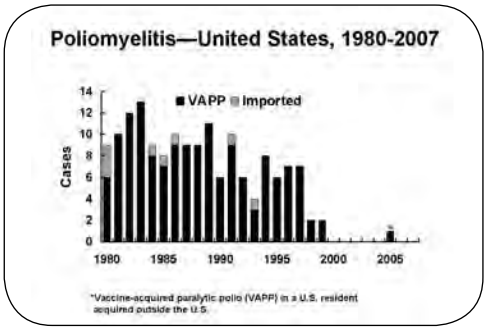
The last cases of paralytic poliomyelitis caused by endemic transmission of wild virus in the United States were in

1979, when an outbreak occurred among the Amish in several Midwest states. The virus was imported from the Netherlands.

From 1980 through 1999, a total of 152 confirmed cases of paralytic poliomyelitis were reported, an average of 8 cases per year. Six cases were acquired outside the United States and imported. The last imported case was reported in 1993. Two cases were classified as indeterminant (no poliovirus isolated from samples obtained from the patients, and patients had no history of recent vaccination or direct contact with a vaccine recipient). The remaining 144 (95%) cases were vaccine-associated paralytic polio (VAPP) caused by live oral polio vaccine.

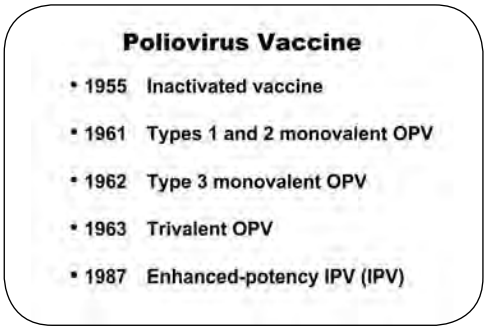
In order to eliminate VAPP from the United States, ACIP recommended in 2000 that IPV be used exclusively in the United States. The last case of VAPP acquired in the United States was reported in 1999. In 2005, an unvaccinated U.S. resident was infected with polio vaccine virus in Costa Rica and subsequently developed VAPP. Also in 2005, several asymptomatic infections with a vaccine-derived poliovirus were detected in unvaccinated children in Minnesota. The source of the vaccine virus has not been determined, but it appeared to have been circulating among humans for at least 2 years based on genetic changes in the virus. No VAPP has been reported from this virus.





Poliovirus Vaccines

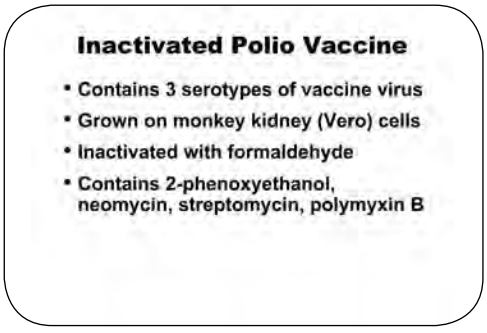
Inactivated poliovirus vaccine (IPV) was licensed in 1955 and was used extensively from that time until the early 1960s. In 1961, type 1 and 2 monovalent oral poliovirus vaccine (MOPV) was licensed, and in 1962, type 3 MOPV was licensed. In 1963, trivalent OPV was licensed and largely replaced IPV use. Trivalent OPV was the vaccine of choice in the United States and most other countries of the world after its introduction in 1963. An enhanced-potency IPV was licensed in November 1987 and first became available in 1988. Use of OPV was discontinued in the United States in 2000.



Characteristics

Inactivated poliovirus vaccine

Two enhanced forms of inactivated poliovirus vaccine are currently licensed in the United States, but only one vaccine (IPOL, sanofi pasteur) is actually distributed. This vaccine contains all three serotypes of polio vaccine virus. The viruses are grown in a type of monkey kidney tissue culture (Vero cell line) and inactivated with formaldehyde. The vaccine contains 2-phenoxyethanol as a preservative, and trace amounts of neomycin, streptomycin, and polymyxin B. It is supplied in a single-dose prefilled syringe and should



be administered by either subcutaneous or intramuscular injection.

Oral poliovirus vaccine

Trivalent OPV contains live attenuated strains of all three serotypes of poliovirus in a 10:1:3 ratio. The vaccine viruses are grown in monkey kidney tissue culture (Vero cell line). The vaccine is supplied as a single 0.5-mL dose in a plastic dispenser. The vaccine contains trace amounts of neomycin and streptomycin. OPV does not contain a preservative.

Oral Polio Vaccine

- Contains 3 serotypes of vaccine virus
- Grown on monkey kidney (Vero) cells
- Contains neomycin and streptomycin
- Shed in stool for up to 6 weeks following vaccination

Live attenuated polioviruses replicate in the intestinal mucosa and lymphoid cells and in lymph nodes that drain the intestine. Vaccine viruses are excreted in the stool of the vaccinated person for up to 6 weeks after a dose. Maximum viral shedding occurs in the first 1–2 weeks after vaccination, particularly after the first dose.

Vaccine viruses may spread from the recipient to contacts. Persons coming in contact with fecal material of a vaccinated person may be exposed and infected with vaccine virus.

Immunogenicity and Vaccine Efficacy

Inactivated poliovirus vaccine

Inactivated Polio Vaccine

- Highly effective in producing immunity to poliovirus
- 90% or more immune after 2 doses
- At least 99% immune after 3 doses
- Duration of immunity not known with certainty

IPV is highly effective in producing immunity to poliovirus and protection from paralytic poliomyelitis. Ninety percent or more of vaccine recipients develop protective antibody to all three poliovirus types after two doses, and at least 99% are immune following three doses. Protection against paralytic disease correlates with the presence of antibody.

IPV appears to produce less local gastrointestinal immunity than does OPV, so persons who receive IPV are more readily infected with wild poliovirus than OPV recipients.

The duration of immunity with IPV is not known with certainty, although it probably provides protection for many years after a complete series.

Oral poliovirus vaccine

Oral Polio Vaccine

- Highly effective in producing immunity to poliovirus
- Approximately 50% immune after 1 dose
- More than 95% immune after 3 doses
- Immunity probably lifelong

OPV is highly effective in producing immunity to poliovirus. A single dose of OPV produces immunity to all three vaccine viruses in approximately 50% of recipients. Three doses produce immunity to all three poliovirus types in more than 95% of recipients. As with other live-virus vaccines, immunity from oral poliovirus vaccine is probably lifelong. OPV produces excellent intestinal immunity, which helps prevent infection with wild virus.

Serologic studies have shown that seroconversion following three doses of either IPV or OPV is nearly 100% to all three

vaccine viruses. However, seroconversion rates after three doses of a combination of IPV and OPV are lower, particularly to type 3 vaccine virus (as low as 85% in one study). A fourth dose (most studies used OPV as the fourth dose) usually produces seroconversion rates similar to three doses of either IPV or OPV.

Vaccination Schedule and Use

Trivalent OPV was the vaccine of choice in the United States (and most other countries of the world) since it was licensed in 1963. The nearly exclusive use of OPV led to elimination of wild-type poliovirus from the United States in less than 20 years. However, one case of VAPP occurred for every 2 to 3 million doses of OPV administered, which resulted in 8 to 10 cases of VAPP each year in the United States (see Adverse Reactions section for more details on VAPP). From 1980 through 1999, VAPP accounted for 95% of all cases of paralytic poliomyelitis reported in the United States.

Polio Vaccination Recommendations, 1996-1999

- Increased use of IPV (sequential IPV-OPV schedule) recommended in 1996
- Intended to *reduce* the risk of vaccine-associated paralytic polio (VAPP)
- Continued risk of VAPP for contacts of OPV recipients

In 1996, ACIP recommended an increase in use of IPV through a sequential schedule of IPV followed by OPV. This recommendation was intended to *reduce* the occurrence of vaccine-associated paralytic polio. The sequential schedule was expected to eliminate VAPP among vaccine recipients by producing humoral immunity to polio vaccine viruses with inactivated polio vaccine prior to exposure to live vaccine virus. Since OPV was still used for the third and fourth doses of the polio vaccination schedule, a risk of VAPP would continue to exist among contacts of vaccinees, who were exposed to live vaccine virus in the stool of vaccine recipients.

Polio Vaccination Recommendations

- Exclusive use of IPV recommended in 2000
- OPV no longer routinely available in the United States
- Indigenous VAPP eliminated

The sequential IPV–OPV polio vaccination schedule was widely accepted by both providers and parents. Fewer cases of VAPP were reported in 1998 and 1999, suggesting an impact of the increased use of IPV. However, only the complete discontinuation of use of OPV would lead to complete elimination of VAPP. To further the goal of complete elimination of paralytic polio in the United States, ACIP recommended in July 1999 that inactivated polio vaccine be used exclusively in the United States beginning in 2000. OPV is no longer routinely available in the United States. Exclusive use of IPV eliminated the shedding of live vaccine virus, and eliminated any indigenous VAPP.

Polio Vaccination Schedule

Age	Vaccine	Minimum Interval
2 months	IPV	---
4 months	IPV	4 weeks
6-18 months	IPV	4 weeks
4-6 years*	IPV	4 weeks

*the fourth dose of IPV may be given as early as 18 weeks of age

A primary series of IPV consists of three doses. In infancy, these primary doses are integrated with the administration of other routinely administered vaccines. The first dose may be given as early as 6 weeks of age but is usually given at 2 months of age, with a second dose at 4 months of age. The third dose should be given at 6–18 months of age. The first and second doses of IPV are necessary to induce a primary immune response, and the third dose of IPV ensures

"boosting" of antibody titers to high levels. The preferred interval between the second and third doses of IPV is 2–8 months. However, if accelerated protection is needed, the minimum interval between all doses of IPV is 4 weeks, and the minimum age for the fourth dose is 18 weeks. Children who receive three doses of IPV before the fourth birthday should receive a fourth dose before or at school entry. The fourth dose is not needed if the third dose is given on or after the fourth birthday. If all four IPV doses are administered after 6 weeks of age and are all separated by at least 4 weeks, a fifth dose is not needed, even if the fourth dose was administered before 4 years of age (except if a specific state school entry requirement mandates a dose of polio vaccine on or after the fourth birthday). It is not necessary to repeat or add doses if the interval between doses is prolonged.

Schedules That Include Both IPV and OPV

- Only IPV is available in the United States
- Schedule begun with OPV should be completed with IPV
- Any combination of 4 doses of IPV and OPV by 4-6 years of age constitutes a complete series

Only IPV is available for routine polio vaccination of children in the United States. A polio vaccination schedule begun with OPV should be completed with IPV. If a child receives both types of vaccine, four doses of any combination of IPV or OPV by 4–6 years of age is considered a complete poliovirus vaccination series. A minimum interval of 4 weeks should separate all doses of the series.

Combination Vaccines That Contain IPV

- Pediarix
  —DTaP, Hepatitis B and IPV
- Kinrix
  —DTaP and IPV
- Pentacel
  —DTaP, Hib and IPV

There are three combination vaccines that contain inactivated polio vaccine. Pediarix is produced by GlaxoSmithKline and contains DTaP, hepatitis B and IPV vaccines. Pediarix is licensed for the first 3 doses of the DTaP series among children 6 weeks through 6 years of age. Kinrix is also produced by GSK and contains DTaP and IPV. Kinrix is licensed only for the fifth dose of DTaP and fourth dose of IPV among children 4 through 6 years of age. Pentacel is produced by sanofi pasteur and contains DTaP, Hib and IPV. It is licensed for the first four doses of the component vaccines among children 6 weeks through 4 years of age. Pentacel is not licensed for children 5 years or older. Additional information about these combination vaccines is in the pertussis chapter of this book.

Polio Vaccination of Adults

Polio Vaccination of Adults

- Routine vaccination of U.S. residents 18 years of age and older not necessary or recommended
- May consider vaccination of travelers to polio-endemic countries and selected laboratory workers

Routine vaccination of adults (18 years of age and older) who reside in the United States is not necessary or recommended because most adults are already immune and have a very small risk of exposure to wild poliovirus in the United States.

Some adults, however, are at increased risk of infection with poliovirus. These include travelers to areas where poliomyelitis is endemic or epidemic (currently limited to South Asia, the eastern Mediterranean, and Africa), laboratory workers handling specimens that may contain polioviruses, and healthcare personnel in close contact with patients who may be excreting wild polioviruses. In addition, members of specific population groups with a current disease caused

by wild polioviruses (e.g., during an outbreak) are also at increased risk.

Recommendations for poliovirus vaccination of adults in the above categories depend upon the previous vaccination history and the time available before protection is required.

- For unvaccinated adults (including adults without a written record of prior polio vaccination) at increased risk of exposure to poliomyelitis, primary immunization with IPV is recommended. The recommended schedule is two doses separated by 1 to 2 months, and a third dose given 6 to 12 months after the second dose.

In some circumstances time will not allow completion of this schedule. If 8 weeks or more are available before protection is needed, three doses of IPV should be given at least 4 weeks apart. If 4 to 8 weeks are available before protection is needed, two doses of IPV should be given at least 4 weeks apart. If less than 4 weeks are available before protection is needed, a single dose of IPV is recommended. In all instances, the remaining doses of vaccine should be given later, at the recommended intervals, if the person remains at increased risk.

Polio Vaccination of Unvaccinated Adults

- IPV
- Use standard IPV schedule if possible (0, 1-2 months, 6-12 months)
- May separate doses by 4 weeks if accelerated schedule needed

- Adults who have previously completed a primary series of 3 or more doses and who are at increased risk of exposure to poliomyelitis should be given one dose of IPV. The need for further supplementary doses has not been established. Only one supplemental dose of polio vaccine is recommended for adults who have received a complete series (i.e., it is not necessary to administer additional doses for subsequent travel to a polio endemic country).

- Adults who have previously received less than a full primary course of OPV or IPV and who are at increased risk of exposure to poliomyelitis should be given the remaining doses of IPV, regardless of the interval since the last dose and type of vaccine previously received. It is not necessary to restart the series of either vaccine if the schedule has been interrupted.

Polio Vaccination of Previously Vaccinated Adults

- Previously complete series
  - —administer one dose of IPV
- Incomplete series
  - —administer remaining doses in series
  - —no need to restart series

Contraindications And Precautions To Vaccination

Severe allergic reaction (anaphylaxis) to a vaccine component, or following a prior dose of vaccine, is a contraindication to further doses of that vaccine. Since IPV contains trace amounts of streptomycin, neomycin, and polymyxin B, there is a possibility of allergic reactions in persons sensitive to these antibiotics. Persons with allergies that are not anaphylactic, such as skin contact sensitivity, may be vaccinated.

Moderate or severe acute illness is a precaution for IPV.

Polio Vaccine Contraindications and Precautions

- Severe allergic reaction to a vaccine component or following a prior dose of vaccine
- Moderate or severe acute illness

Breastfeeding does not interfere with successful immunization against poliomyelitis with IPV. IPV may be administered to a child with diarrhea. Minor upper respiratory illnesses with or without fever, mild to moderate local reactions to a prior dose of vaccine, current antimicrobial therapy, and the convalescent phase of an acute illness are not contraindications for vaccination with IPV.

Contraindications to combination vaccines that contain IPV are the same as the contraindications to the individual components (e.g., DTaP, hepatitis B).

Adverse Reactions Following Vaccination

Minor local reactions (pain, redness) may occur following IPV. No serious adverse reactions to IPV have been documented. Because IPV contains trace amounts of streptomycin, polymyxin B, and neomycin, allergic reactions may occur in persons sensitive to these antibiotics.

Polio Vaccine Adverse Reactions

- Rare local reactions (IPV)
- No serious reactions to IPV have been documented
- Paralytic poliomyelitis (OPV)

Vaccine-Associated Paralytic Poliomyelitis

Vaccine-associated paralytic polio is a rare adverse reaction following live oral poliovirus vaccine. Inactivated poliovirus vaccine does not contain live virus, so it cannot cause VAPP. The mechanism of VAPP is believed to be a mutation, or reversion, of the vaccine virus to a more neurotropic form. These mutated viruses are called revertants. Reversion is believed to occur in almost all vaccine recipients, but it only rarely results in paralytic disease. The paralysis that results is identical to that caused by wild virus, and may be permanent.

Vaccine-Associated Paralytic Polio

- Increased risk in persons 18 years and older
- Increased risk in persons with immunodeficiency
- No procedure available for identifying persons at risk of paralytic disease
- 5-10 cases per year with exclusive use of OPV
- Most cases in healthy children and their household contacts

VAPP is more likely to occur in persons 18 years of age and older than in children, and is much more likely to occur in immunodeficient children than in those who are immunocompetent. Compared with immunocompetent children, the risk of VAPP is almost 7,000 times higher for persons with certain types of immunodeficiencies, particularly B-lymphocyte disorders (e.g., agammaglobulinemia and hypogammaglobulinemia), which reduce the synthesis of immune globulins. There is no procedure available for identifying persons at risk of paralytic disease, except excluding older persons and screening for immunodeficiency.

Vaccine-Associated Paralytic Polio (VAPP) 1980-1998

• Healthy recipients of OPV	41%
• Healthy contacts of OPV recipients	31%
• Community acquired	5%
• Immunodeficient	24%

From 1980 through 1998, 152 cases of paralytic polio were reported in the United States; 144 (95%) of these cases were VAPP, and the remaining eight were in persons who acquired documented or presumed wild-virus polio outside the United States. Of the 144 VAPP cases, 59 (41%) occurred in healthy vaccine recipients (average age 3 months). Forty-four (31%) occurred in healthy contacts of vaccine recipients (average age 26 years), and 7 (5%) were community acquired (i.e.,

vaccine virus was recovered but there was no known contact with a vaccine recipient). Thirty-four (24%) of VAPP cases occurred in persons with immunologic abnormalities (27 in vaccine recipients and 7 in contacts of vaccine recipients). None of the vaccine recipients were known to be immunologically abnormal prior to vaccination.

The risk of VAPP is not equal for all OPV doses in the vaccination series. The risk of VAPP is 7 to 21 times higher for the first dose than for any other dose in the OPV series. From 1980 through 1994, 303 million doses of OPV were distributed and 125 cases of VAPP were reported, for an overall risk of VAPP of one case per 2.4 million doses. Forty-nine paralytic cases were reported among immunocompetent recipients of OPV during this period. The overall risk to these recipients was one VAPP case per 6.2 million OPV doses. However, 40 (82%) of these 49 cases occurred following receipt of the first dose, making the risk of VAPP one case per 1.4 million first doses. The risk for all other doses was one per 27.2 million doses. The reason for this difference by dose is not known with certainty, but it is probably because the vaccine virus is able to replicate longer in a completely nonimmune infant. This prolonged replication increases the chance of the emergence of a revertant virus that may cause paralysis. The situation is similar for contacts. A nonimmune child may shed virus longer, increasing the chance of exposure of a contact.

The last case of VAPP acquired in the United States was reported in 1999. As noted previously, a U.S. resident with VAPP was reported in 2005, but the vaccine virus infection was acquired in Costa Rica.

Vaccine Storage and Handling

IPV may be shipped without refrigeration provided it is delivered within 4 days. It should be maintained at 35°–46°F (2°–8°C). The vaccine should be clear and colorless. Any vaccine showing particulate matter, turbidity, or change in color should be discarded.

Outbreak Investigation and Control

Collect preliminary clinical and epidemiologic information (including vaccine history and contact with OPV vaccines) on any suspected case of paralytic polio. Notify CDC, (404-639-8255) after appropriate local and state health authorities have been notified. Intensify field investigation to verify information and collect appropriate specimens for viral isolation and serology.

A single case of paralytic poliomyelitis demands immediate attention. If the evidence indicates vaccine-associated disease, no outbreak control program is needed. If, however, evidence indicates wild virus (for example, two cases in a

community), all unvaccinated persons in the epidemic area who are 6 weeks of age and older and whose vaccine histories are uncertain should be vaccinated.

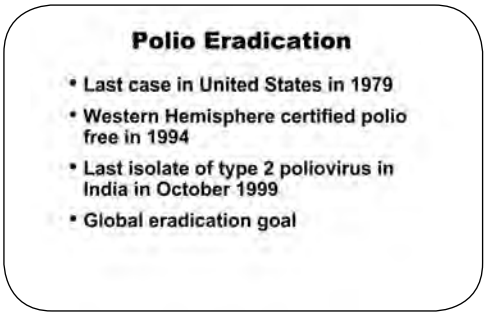
Polio Eradication

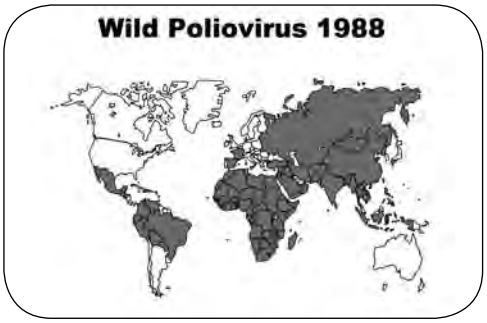
Following the widespread use of poliovirus vaccine in the mid-1950s, the incidence of poliomyelitis declined rapidly in many industrialized countries. In the United States, the number of cases of paralytic poliomyelitis reported annually declined from more than 20,000 cases in 1952 to fewer than 100 cases in the mid-1960s. The last documented indigenous transmission of wild poliovirus in the United States was in 1979.

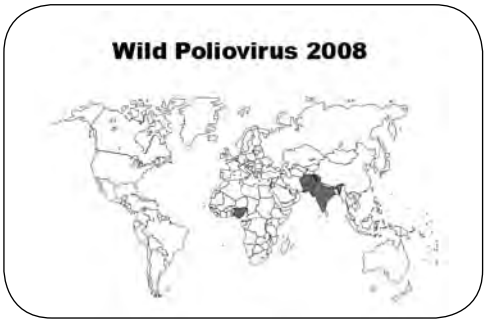
In 1985, the member countries of the Pan American Health Organization adopted the goal of eliminating poliomyelitis from the Western Hemisphere by 1990. The strategy to achieve this goal included increasing vaccination coverage; enhancing surveillance for suspected cases (i.e., surveillance for acute flaccid paralysis); and using supplemental immunization strategies such as national immunization days, house-to-house vaccination, and containment activities. Since 1991, when the last wild-virus–associated indigenous case was reported from Peru, no additional cases of poliomyelitis have been confirmed despite intensive surveillance. In September 1994, an international commission certified the Western Hemisphere to be free of indigenous wild poliovirus. The commission based its judgment on detailed reports from national certification commissions that had been convened in every country in the region.

In 1988, the World Health Assembly (the governing body of the World Health Organization) adopted the goal of global eradication of poliovirus by the year 2000. Although this goal was not achieved, substantial progress has been made. One type of poliovirus appears to have already been eradicated. In 1988, an estimated 350,000 cases of paralytic polio occurred, and the disease was endemic in more than 125 countries. By 2006, fewer than 2,000 cases were reported globally—a reduction of more than 99% from 1988—and polio remained endemic in only four countries. In addition, one type of poliovirus appears to have already been eradicated. The last isolation of type 2 virus was in India in October 1999.

The polio eradication initiative is led by a coalition of international organizations that includes WHO, the United Nations Children's Fund (UNICEF), CDC, and Rotary International. Other bilateral and multilateral organizations also support the initiative. Rotary International has contributed more than $600 million to support the eradication initiative. Current information on the status of the global polio eradication initiative is available on the World Health Organization website at www.polioeradication.org/.







Postpolio Syndrome

After an interval of 30–40 years, 25%–40% of persons who contracted paralytic poliomyelitis in childhood experience new muscle pain and exacerbation of existing weakness, or develop new weakness or paralysis. This disease entity is referred to as postpolio syndrome. Factors that increase the risk of postpolio syndrome include increasing length of time since acute poliovirus infection, presence of permanent residual impairment after recovery from the acute illness, and female sex. The pathogenesis of postpolio syndrome is thought to involve the failure of oversized motor units created during the recovery process of paralytic poliomyelitis. Postpolio syndrome is not an infectious process, and persons experiencing the syndrome do not shed poliovirus.

For more information, or for support for persons with postpolio syndrome and their families, contact:

Post-Polio Health International
4207 Lindell Boulevard #110
St. Louis, MO 63108-2915
314-534-0475

www.post-polio.org

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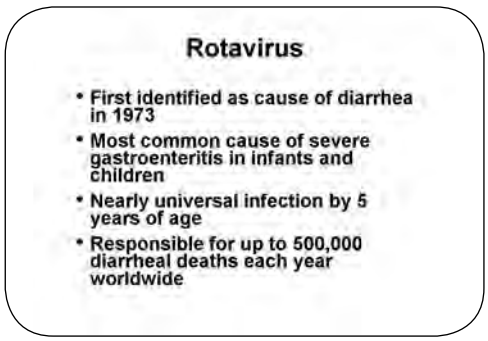
CDC. Apparent global interruption of wild poliovirus type 2 transmission. *MMWR* 2001;50:222–4.

Poliomyelitis

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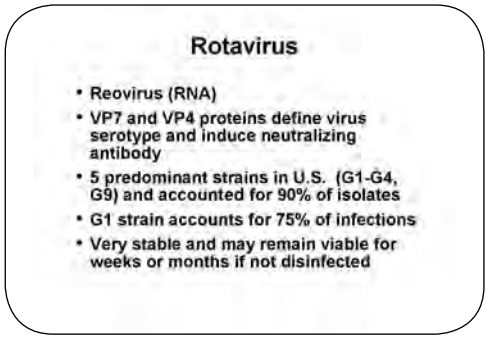
Rotavirus

Diarrheal disease has been recognized in humans since antiquity.Until the early 1970s, a bacterial, viral, or parasitic etiology of diarrheal disease in children could be detected in fewer than 30% of cases. In 1973, Bishop and colleagues observed a virus particle in the intestinal tissue of children with diarrhea by using electron micrography. This virus was subsequently called "rotavirus" because of its similarity in appearance to a wheel (*rota* is Latin for wheel). By 1980, rotavirus was recognized as the most common cause of severe gastroenteritis in infants and young children in the United States. It is now known that infection with rotavirus is nearly universal, with almost all children infected by 5 years of age. Rotavirus is responsible for 20–60 deaths per year in the United States and up to 500,000 deaths from diarrhea worldwide. A vaccine to prevent rotavirus gastroenteritis was first licensed in August 1998 but was withdrawn in 1999 because of its association with intussusception. Second-generation vaccines were licensed in 2006 and 2008.



Rotavirus

Rotavirus is a double-stranded RNA virus of the family *Reoviridae*. The virus is composed of three concentric shells that enclose 11 gene segments. The outermost shell contains two important proteins—VP7, or G-protein, and VP4, or P-protein. VP7 and VP4 define the serotype of the virus and induce neutralizing antibody that is probably involved in immune protection. From 1996 through 2005, five strains of rotavirus (G1–4, G9) accounted for 90% of isolates from children younger than 5 years in the United States. Of these, the G1 strain accounted for more than 75% of isolates.

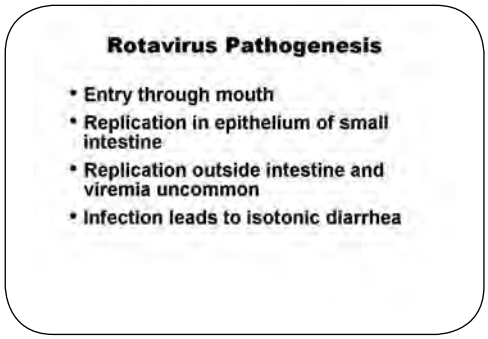


Rotavirus is very stable and may remain viable in the environment for weeks or months if not disinfected.

Rotaviruses cause infection in many species of mammals, including cows and monkeys. These animal strains are antigenically distinct from those causing human infection, and they rarely cause infection in humans.

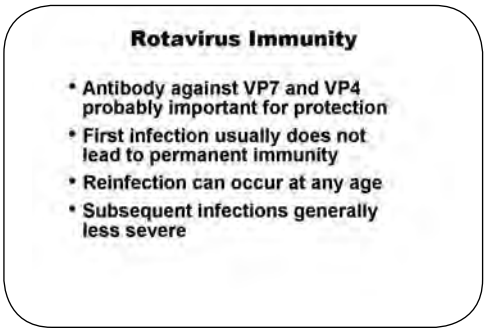
Pathogenesis

The virus enters the body through the mouth. Viral replication occurs in the villous epithelium of the small intestine. Replication outside the small intestine and systemic spread of the virus (viremia) are believed to be uncommon in immunocompetent persons. Infection may result in decreased intestinal absorption of sodium, glucose, and water, and decreased levels of intestinal lactase, alkaline phosphatase, and sucrase activity, and may lead to isotonic diarrhea.



The immune correlates of protection from rotavirus are poorly understood. Serum and mucosal antibodies against

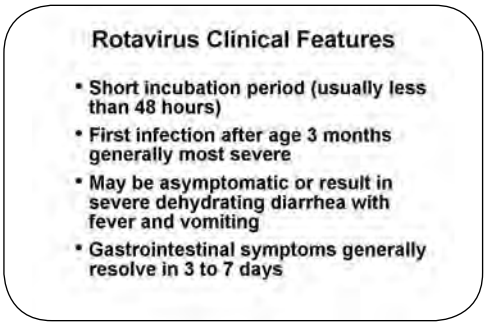
Rotavirus



VP7 and VP4 are probably important for protection from disease. Cell-mediated immunity probably plays a role in recovery from infection and in protection.

Recovery from a first rotavirus infection usually does not lead to permanent immunity. After a single natural infection, 38% of children are protected against any subsequent rotavirus infection, 77% are protected against rotavirus diarrhea, and 87% are protected against severe diarrhea. Reinfection can occur at any age. Subsequent infections confer progressively greater protection and are generally less severe than the first. Recurrent rotavirus infections affect persons of all ages. Recurrent infections are usually asymptomatic or result in mild diarrhea that may be preceded or accompanied by vomiting and low-grade fever.

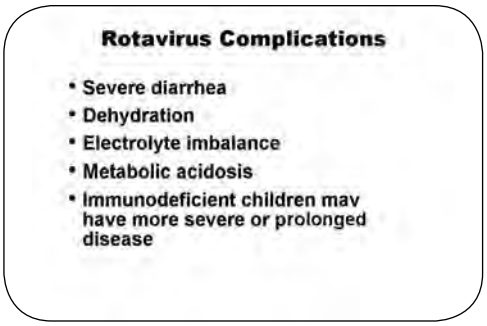
Clinical Features



The incubation period for rotavirus diarrhea is short, usually less than 48 hours. The clinical manifestations of infection vary and depend on whether it is the first infection or reinfection. The first infection after 3 months of age is generally the most severe. Infection may be asymptomatic, may cause self-limited watery diarrhea, or may result in severe dehydrating diarrhea with fever and vomiting. Up to one-third of infected children may have a temperature greater than 102°F (39°C). The gastrointestinal symptoms generally resolve in 3 to 7 days.

The clinical features and stool characteristics of rotavirus diarrhea are nonspecific, and similar illness may be caused by other pathogens. As a result, confirmation of a diarrheal illness as rotavirus requires laboratory testing.

Complications



Rotavirus infection in infants and young children can lead to severe diarrhea, dehydration, electrolyte imbalance, and metabolic acidosis. Children who are immunocompromised because of congenital immunodeficiency or because of bone marrow or solid organ transplantation may experience severe or prolonged rotavirus gastroenteritis and may have evidence of abnormalities in multiple organ systems, particularly the kidney and liver.

Laboratory Diagnosis

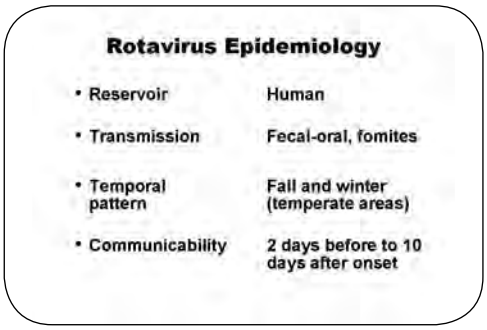
The most widely available method for confirmation of rotavirus infection is detection of rotavirus antigen in stool by enzyme immunoassay (EIA). Several commercial test kits are available that detect an antigen common to human rotaviruses. These kits are simple to use, inexpensive, and very sensitive. Other techniques (such as electron microscopy, reverse transcription polymerase chain reaction, nucleic acid hybridization, sequence analysis, and culture)

are used primarily in research settings. Rotavirus antigen has also been identified in the serum of patients 3–7 days after disease onset, but at present, routine diagnostic testing is based primarily on testing of fecal specimens.

Epidemiology

Occurrence

Rotavirus occurs throughout the world. The prevalence of rotavirus strains varies by geographic area, and strains not included in the vaccine are present in some parts of the world.



Reservoir

The reservoir of rotavirus is the gastrointestinal tract and stool of infected humans. Although rotavirus infection occurs in many nonhuman mammals, transmission of animal rotaviruses to humans is believed to be rare and probably does not lead to clinical illness. Although immunodeficient persons may shed rotavirus for a prolonged period, a true carrier state has not been described.

Transmission

Rotaviruses are shed in high concentration in the stool of infected persons. Transmission is by fecal-oral spread, both through close person-to-person contact and by fomites (such as toys and other environmental surfaces contaminated by stool). Rotaviruses are also probably transmitted by other modes such as fecally contaminated food and water and respiratory droplets.

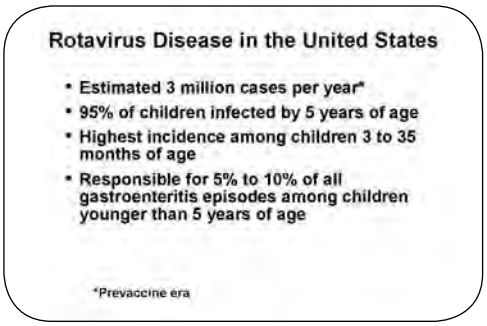
Temporal Pattern

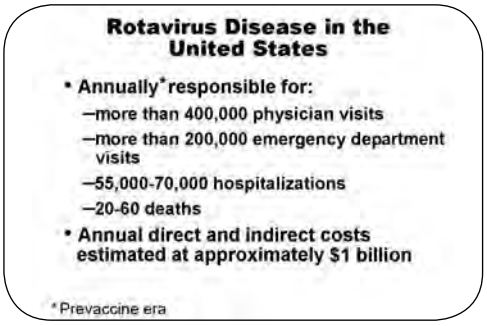
In temperate climates, disease is more prevalent during fall and winter. In the United States, annual epidemic peaks usually progress from the Southwest during November and December and spread to the Northeast by April and May. The reason for this seasonal pattern is unknown. In tropical climates, the disease is less seasonal than in temperate areas.

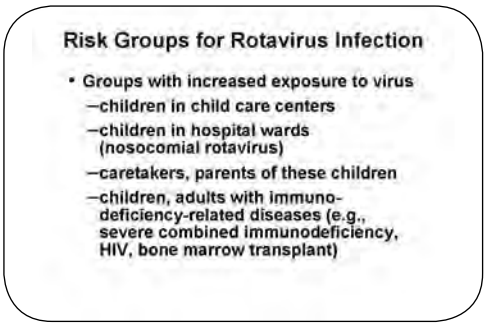
Communicability

Rotavirus is highly communicable, as evidenced by the nearly universal infection of children by age 5 years. Infected persons shed large quantities of virus in their stool beginning 2 days before the onset of diarrhea and for up to 10 days after onset of symptoms. Rotavirus may be detected in the stool of immunodeficient persons for more than 30 days after infection. Spread within families, institutions, hospitals, and child care settings is common.

Rotavirus







Secular Trends in the United States

Rotavirus infection is not nationally notifiable in the United States. Estimates of incidence and disease burden are based on special surveys, cohort studies, and hospital discharge data.

Rotavirus infection is nearly universal. In the prevaccine era an estimated 3 million rotavirus infections occurred every year in the United States and 95% of children experienced at least one rotavirus infection by age 5 years. The incidence of rotavirus is similar in developed and developing countries, suggesting that improved sanitation alone is not sufficient to prevent the infection.

Infants younger than 3 months of age have relatively low rates of rotavirus infection, probably because of passive maternal antibody, and possibly breastfeeding. The incidence of clinical illness is highest among children 3 to 35 months of age. Rotavirus infection of adults is usually asymptomatic but may cause diarrheal illness.

In the United States, rotaviruses are responsible for 5% to 10% of all gastroenteritis episodes among children younger than 5 years of age. However, they are the most common cause of severe diarrheal disease and account for a higher proportion of severe episodes leading to clinic or hospital visits. Rotavirus accounts for 30% to 50% of all hospitalizations for gastroenteritis among U.S. children younger than 5 years of age, and more than 70% of hospitalizations for gastroenteritis during the seasonal peaks.

In the prevaccine era rotavirus infection was responsible for more than 400,000 physician visits, more than 200,000 emergency department (ED) visits, 55,000 to 70,000 hospitalizations each year, and 20 to 60 deaths. Annual direct and indirect costs were estimated at approximately $1 billion, primarily due to the cost of time lost from work to care for an ill child.

Groups at increased risk for rotavirus infection are those with increased exposure to virus. These include children who attend child care centers, children in hospital wards (nosocomial rotavirus), caretakers and parents of children in child care or hospitals, and children and adults with immunodeficiency-related diseases (e.g., severe combined immunodeficiency disease (SCID), HIV, bone marrow transplant).

Rotavirus Vaccines

The first rotavirus vaccines were derived from either bovine (cow) or rhesus (monkey) origin. Studies demonstrated that these live oral vaccines could prevent rotavirus diarrhea in young children, but efficacy varied widely. Because immunity to G (VP7) or P (VP4) proteins was associated with disease protection and recovery, new live virus vaccines

were developed that incorporated G proteins or both G and P proteins for each of the predominant serotypes.

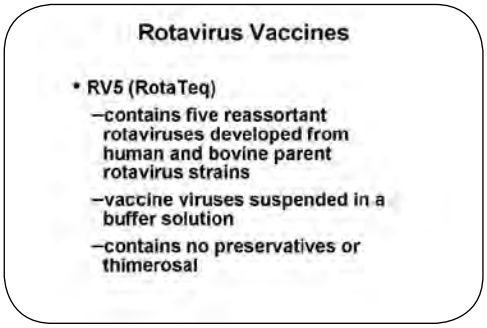
In 1998, a rhesus-based tetravalent rotavirus vaccine (RRV-TV, Rotashield) was licensed and recommended for routine immunization of U.S. infants. However, RRV-TV was withdrawn from the U.S. market within 1 year of its introduction because of its association with intussusception. The risk of intussusception was most elevated (more than a 20-fold increase) within 3 to 14 days after receipt of the first dose of RRV-TV, with a smaller (approximately 5-fold) increase in risk within 3 to 14 days after the second dose. Overall, the risk associated with the first dose of RRV-TV was estimated to be about one case per 10,000 vaccine recipients. Some researchers have suggested that the risk of intussusception associated with RRV-TV was age-dependent and that the absolute number of intussusception events, and possibly the relative risk of intussusception associated with the first dose of RRV-TV, increased with increasing age at vaccination.

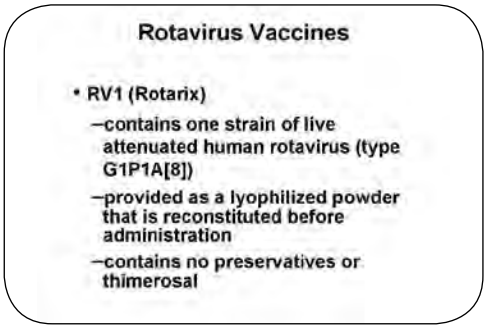
Characteristics

There are currently two rotavirus vaccines licensed for use in the United States. RV5 (RotaTeq) is a live oral vaccine manufactured by Merck and licensed by the Food and Drug Administration in February 2006. RV5 contains five reassortant rotaviruses developed from human and bovine parent rotavirus strains. Each 2-mL vial of vaccine contains approximately 2 x 10^6 infectious units of each of the five reassortant strains. The vaccine viruses are suspended in a buffer solution that contains sucrose, sodium citrate, sodium phosphate monobasic monohydrate, sodium hydroxide, polysorbate 80, and tissue culture media. Trace amounts of fetal bovine serum might be present. The vaccine contains no preservatives or thimerosal.

Fecal shedding of vaccine virus was evaluated in a subset of persons enrolled in the phase III trials. Vaccine virus was shed by 9% of 360 infants after dose 1, but none of 249 and 385 infants after doses 2 and 3, respectively. Shedding was observed as early as 1 day and as late as 15 days after a dose. The potential for transmission of vaccine virus was not assessed.

RV1 (Rotarix), a live oral vaccine manufactured by GlaxoSmithKline, was licensed by the FDA in April 2008. RV1 contains one strain of live attenuated human strain 89-12 (type G1P1A[8]) rotavirus. RV1 is provided as a lyophilized powder that is reconstituted before administration. Each 1-mL dose of reconstituted vaccine contains at least 10^6 median cell culture infective units of virus. The vaccine contains amino acids, dextran, Dulbecco's modified Eagle medium, sorbitol and sucrose. The diluent contains calcium





carbonate, sterile water and xanthan. The vaccine contains no preservatives or thimerosal.

Fecal shedding of rotavirus antigen was evaluated in all or a subset of infants from seven studies in various countries. After dose 1, rotavirus antigen shedding was detected by ELISA in 50% to 80% (depending on the study) of infants at approximately day 7 and 0 to 24% at approximately day 30. After dose 2, rotavirus antigen shedding was detected in 4% to 18% of infants at approximately day 7, and 0 to 1.2% at approximately day 30. The potential for transmission of vaccine virus to others was not assessed.

Vaccine Effectiveness

Phase III clinical trials of RV5 (Rotateq) efficacy have involved more than 70,000 infants 6 through 12 weeks of age in 11 countries.

Rotavirus Vaccine Effectiveness

Condition	Effectiveness
Any rotavirus gastroenteritis	74%-87%
Severe gastroenteritis	85%-98%

Both vaccines significantly reduced physician visits for diarrhea, and reduced rotavirus-related hospitalization

After completion of a three-dose RV5 regimen, the efficacy of rotavirus vaccine against rotavirus gastroenteritis of any severity was 74%, and against severe rotavirus gastroenteritis (defined by severity of fever, vomiting, diarrhea and changes in behavior) was 98%. Vaccine efficacy varied by rotavirus serotype.

In a large study, the efficacy of RV5 vaccine against rotavirus gastroenteritis requiring office visits was evaluated among 5,673 children, and efficacy against rotavirus gastroenteritis requiring ED visits and hospitalizations was evaluated among 68,038 children during the first 2 years of life. RV5 vaccine reduced the incidence of office visits by 86%, ED visits by 94%, and hospitalizations for rotavirus gastroenteritis by 96%. The efficacy of fewer than three doses is not known.

Phase III clinical trials of RV1 (Rotarix) efficacy have involved more than 21,000 infants 6 through 12 weeks of age, primarily in two studies in Latin America and Europe.

After completion of a two-dose RV1 regimen, the efficacy of rotavirus vaccine against severe rotavirus gastroenteritis (Latin America study) was 85%, and against any rotavirus gastroenteritis (Europe study) was 87%. RV1 reduced hospitalization for rotavirus gastroenteritis by 85% to 100% (depending on the study). The efficacy of fewer than two doses is not known.

Duration of Immunity

The duration of immunity from rotavirus vaccine is not known. Efficacy through 2 rotavirus seasons has been studied for both vaccines. In general efficacy is lower in the second season than in the first.

Vaccination Schedule and Use

Revised ACIP recommendations for the use of rotavirus vaccine were published in *MMWR* in February 2009. Because of similar estimates of efficacy and safety, neither The Advisory Committee on Immunization Practices (ACIP) nor the Academies of Pediatrics or Family Physicians state a preference for one vaccine versus the other.

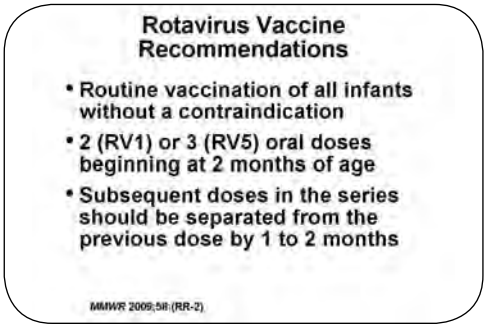
ACIP recommends routine rotavirus vaccination of all infants without a contraindication. The vaccine should be administered as a series of either two or three oral doses, for RV1 and RV5, respectively, beginning at 2 months of age. The vaccination series for both vaccines may be started as early as 6 weeks of age. Subsequent doses in the series should be separated from the previous dose by 1 to 2 months. Rotavirus vaccine should be given at the same visit as other vaccines given at these ages.

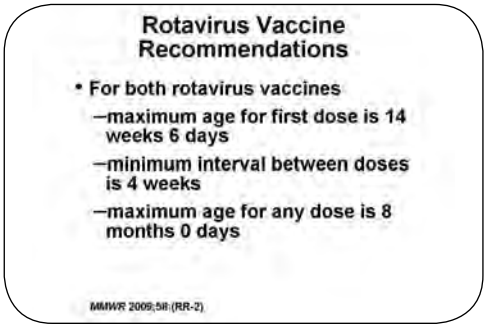
The maximum age for any dose of RV1 approved by the FDA is 24 weeks, while the maximum FDA-approved age for any dose of RV5 is 32 weeks. This difference, as well as the different number of doses in the series could complicate decisions by clinicians who encounter children who received a brand of rotavirus vaccine other than the brand the clinician has in stock. There are currently no data on schedules that include both RV1 and RV5.

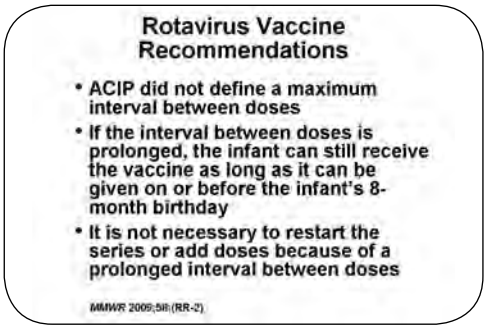
The ACIP developed age recommendations that vary from those of the manufacturers. ACIP recommendations state that the maximum age for the first dose of both vaccines is 14 weeks 6 days. This is an off-label recommendation for RV5 since the approved maximum age for the first dose of that vaccine is 12 weeks. The minimum interval between doses of both rotavirus vaccines is 4 weeks. The maximum age for any dose of either rotavirus vaccine is 8 months 0 days. No rotavirus vaccine should be administered to infants older than 8 months 0 days of age. This is an off-label recommendation for both vaccines, because the labeled maximum age for RV1 is 24 weeks, and the labeled maximum age for RV5 is 32 weeks.

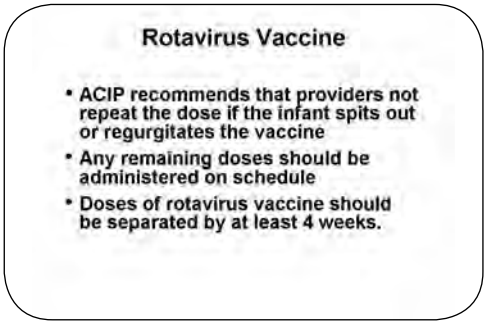
ACIP did NOT define a maximum interval between doses. It is preferable to adhere to the recommended interval of 8 weeks. But if the interval is prolonged, the infant can still receive the vaccine as long as it can be given on or before the 8-month birthday. It is not necessary to restart the series or add doses because of a prolonged interval between doses.

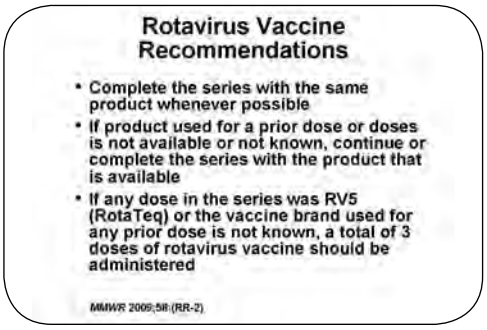
There are few data on the safety or efficacy of giving more than one dose, even partial doses, close together. ACIP recommends that providers not repeat the dose if the infant spits out or regurgitates the vaccine. Any remaining doses should be administered on schedule. Doses of rotavirus vaccine should be separated by at least 4 weeks.





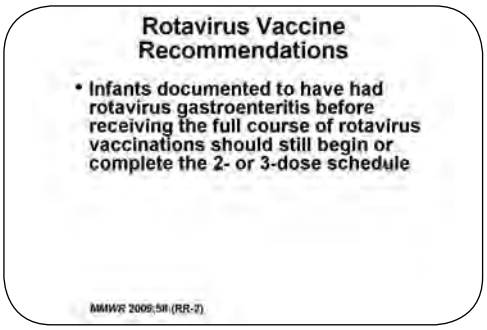






ACIP recommends that the rotavirus vaccine series should be completed with the same product whenever possible. However, vaccination should not be deferred if the product used for a prior dose or doses is not available or is not known. In this situation, the provider should continue or complete the series with the product that is available. If any dose in the series was RV5 (RotaTeq) or the vaccine brand used for any prior dose in the series is not known, a total of three doses of rotavirus vaccine should be administered.

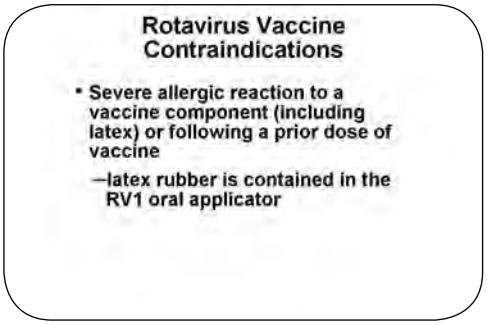
Breastfeeding does not appear to diminish immune response to rotavirus vaccine. Infants who are being breastfed should be vaccinated on schedule.



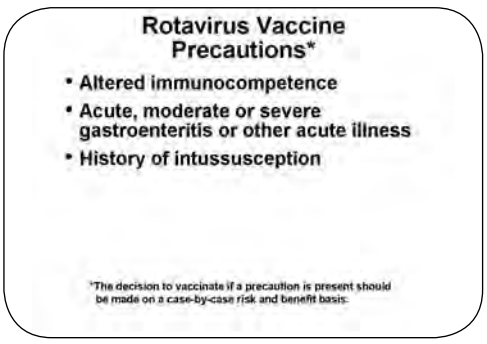
There are at least 5 serotypes of rotavirus that may cause diarrheal disease in the United States. In addition, infants may experience multiple episodes of rotavirus diarrhea because the initial infection may provide only partial immunity. Infants documented to have had rotavirus gastroenteritis before receiving the full course of rotavirus vaccinations should still begin or complete the 2- or 3-dose schedule.

Contraindications and Precautions to Vaccination

Rotavirus vaccine is contraindicated for infants who are known to have had a severe allergic reaction (anaphylactic) to a vaccine component or following a prior dose of vaccine. Latex rubber is contained in the RV1 oral applicator, so infants with a severe allergy to latex should not receive RV1. The RV5 dosing tube is latex free.



Precaution conditions are those that may increase the chance of a vaccine adverse reaction or reduce the efficacy of the vaccine. In general, infants with precautions to vaccination, described below, should not receive the vaccine until the condition improves unless the benefit of vaccination outweighs the risk of an adverse reaction. However, clinicians may consider use of the vaccine on a case-by-case basis.

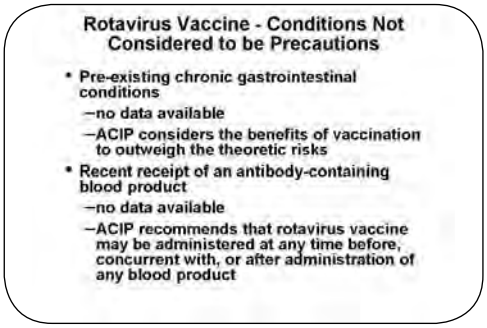


Children who are immunocompromised because of congenital immunodeficiency, or hematopoietic stem cell or solid organ transplantation sometimes experience severe, prolonged, and even fatal rotavirus gastroenteritis. However, no safety or efficacy data are available regarding administration of rotavirus vaccine to infants who are, or are potentially immunocompromised due to either disease or drugs. Clinicians will need to use their judgment in this situation.

There are no data on the use of rotavirus vaccine among infants who are exposed to or infected with HIV. However, two considerations support vaccination of these infants.

First, the HIV diagnosis might not be established in infants born to HIV-infected mothers by the time they reach the age of the first rotavirus vaccine dose. Only 3% percent or less of HIV-exposed infants in the United States will be determined to be HIV infected. Second, vaccine strains of rotavirus are considerably attenuated, and exposure to an attenuated rotavirus is preferable to exposure to wild-type rotavirus.

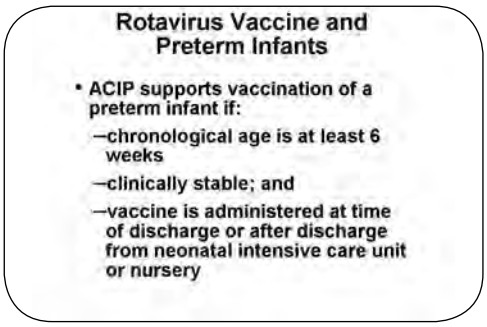
Rotavirus vaccine should generally not be administered to infants with acute, moderate or severe gastroenteritis, or other acute illness until the condition improves. However, infants with mild acute gastroenteritis or other mild acute illness can be vaccinated, particularly if the delay in vaccination will delay the first dose of vaccine beyond 15 weeks 0 days of age.



Available data suggest that infants with a history of intussusception might be at higher risk for a repeat episode than other infants. Until postlicensure data on the safety of rotavirus vaccine are available, the risks for and the benefits of vaccination should be considered when vaccinating infants with a previous episode of intussusception.

No data are available on the immune response to rotavirus vaccine in infants who have recently received a blood product. In theory, infants who have recently received an antibody-containing blood product might have a reduced immunologic response to a dose of oral rotavirus vaccine. However, 2 or 3 doses of vaccine are administered in the full rotavirus vaccine series, and no increased risk for adverse events is expected. ACIP now recommends that rotavirus vaccine may be administered at any time before, concurrent with, or after administration of any blood product.

Available data suggest that preterm infants (i.e., infants born at less than 37 weeks' gestation) are at increased risk for hospitalization from rotavirus during the first 1 to 2 years of life. In clinical trials, rotavirus vaccine appeared to be generally well tolerated in preterm infants, although a relatively small number of preterm infants have been evaluated. ACIP considers the benefits of rotavirus vaccination of preterm infants to outweigh the risks of adverse events. ACIP supports vaccination of a preterm infant according to the same schedule and precautions as a full-term infant, provided the following conditions are met: the infant's chronological age is at least 6 weeks, the infant is clinically stable, and the vaccine is administered at the time of discharge or after discharge from the neonatal intensive care unit or nursery. Although the lower level of maternal antibody to rotavirus in very preterm infants theoretically could increase the risk for adverse reactions from rotavirus vaccine, ACIP believes the benefits of vaccinating the infant when age eligible, clinically stable, and no longer in the hospital outweigh the theoretic risks.



Vaccine strains of rotavirus are shed in the feces of vaccinated infants. So if an infant were to be vaccinated with rotavirus vaccine while still needing care in the hospital, a theoretic risk exists for vaccine virus being transmitted to infants in the same unit who are acutely ill, and to preterm infants who are not age eligible for vaccine. ACIP considers that, in usual circumstances, the risk from shedding outweighs the benefit of vaccinating an infant who will remain in the hospital and recommends that these infants not be vaccinated until they meet the conditions described above.

Immunosuppressed Household Contacts of Rotavirus Vaccine Recipients

- Infants living in households with persons who have or are suspected of having an immunodeficiency disorder or impaired immune status can be vaccinated
- Protection provided by vaccinating the infant outweighs the small risk of transmitting vaccine virus

Although rotavirus is shed in the feces of vaccinated infants transmission of vaccine virus has not been documented. Infants living in households with persons who have or are suspected of having an immunodeficiency disorder or impaired immune status can be vaccinated. ACIP believes that the indirect protection of the immunocompromised household member provided by vaccinating the infant in the household, and thereby preventing wild-type rotavirus disease, outweighs the small risk for transmitting vaccine virus to the immunocompromised household member.

Pregnant Household Contacts of Rotavirus Vaccine Recipients

- Infants living in households with pregnant women should be vaccinated
  - —majority of women of childbearing age have pre-existing immunity to rotavirus
  - —risk for infection by vaccine virus is considered to be very low

Infants living in households with pregnant women should be vaccinated according to the same schedule as infants in households without pregnant women. Because the majority of women of childbearing age have preexisting immunity to rotavirus, the risk for infection by the attenuated vaccine virus is considered to be very low. Although transmission of vaccine virus has not been documented, it is prudent for all members of the household to employ measures such as good hand washing after changing a diaper or otherwise coming in contact with the feces of the vaccinated infant.

Adverse Reactions Following Vaccination

Intussusception

Rotavirus Vaccine and Intussusception*

	No. of Infants	Vaccine Recipients	Placebo Recipients
RV1	63,225	7 cases	7 cases
RV5	69,625	6 cases	5 cases

*RV1- 0-30 days after either dose
RV5- 0-42 days after any dose

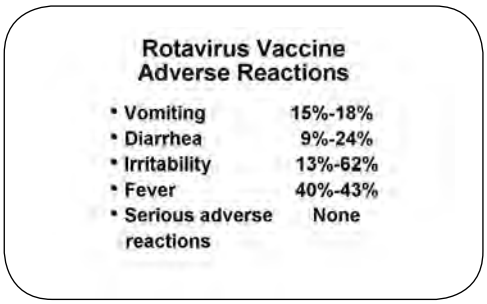
The phase 3 clinical trials of both vaccines were very large, primarily to be able to study the occurrence of intussusception in both vaccine and placebo recipients. The RV1 trials included more than 63,000 infants, of whom half received vaccine and half received a placebo. In the 30 days following either vaccine dose there were 7 cases of intussusception among the vaccine recipients and 7 cases diagnosed among the placebo recipients. The RV5 clinical trials included more than 69,000 infants, of whom half received vaccine and half received a placebo. In the 42 days after vaccination 6 cases of intussusception were diagnosed among the vaccinated infants and 5 cases were diagnosed among the placebo recipients.

These data indicate the background incidence of intussusception in infants, as evidenced by its occurrence in

infants who received a placebo. They also show that while intussusception is to be expected in recipients of rotavirus vaccine, the risk is no higher than among children who are not vaccinated.

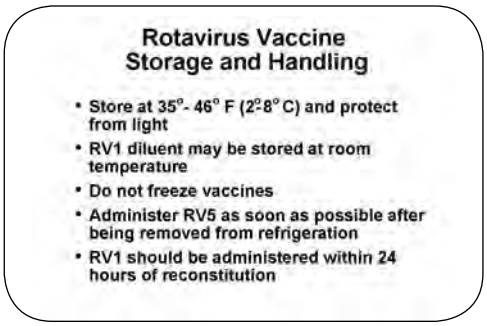
Other Adverse Events

A variety of other adverse reactions were reported during the 7 or 8 days after rotavirus vaccination in the clinical trials, including vomiting in 15% to 18%, diarrhea in 9% to 24%, irritability in 13% to 62%, and fever in 40% to 43%. However, the rate of these symptoms in vaccinated children was similar to the rate in unvaccinated children. No serious adverse reactions attributable to rotavirus vaccine have been reported.



Vaccine Storage and Handling

Both rotavirus vaccines must be stored at refrigerator temperatures (35°–46°F [2°–8°C]) and protected from light. RV1 diluent may be stored at room temperature. The vaccines must not be frozen. The shelf life of properly stored vaccine is 24 months. RV5 should be administered as soon as possible after being removed from refrigeration. RV1 should be administered within 24 hours of reconstitution. Reconstituted RV1 may be stored at refrigerator or room temperature.



Healthcare personnel may be concerned about exposure to vaccine virus during administration of rotavirus vaccine or contact with vaccinated infants. Hand hygiene using soap and water or alcohol-based hand cleaners should already be standard practice wherever vaccines are being administered. This practice should minimize the risk of transmission of rotavirus vaccine virus during administration. Therefore, there are no restrictions on immunosuppressed or pregnant healthcare personnel administering the vaccine.

Rotavirus Surveillance

Rotavirus gastroenteritis is not a reportable disease in the United States, and testing for rotavirus infection is not always performed when a child seeks medical care for acute gastroenteritis. Rotavirus disease surveillance systems need to be adequately sensitive and specific to document the effectiveness of the vaccination program. Methods of surveillance for rotavirus disease at the national level include review of national hospital discharge databases for rotavirus-specific or rotavirus-compatible diagnoses, surveillance for rotavirus disease at three sites that participate in the New Vaccine Surveillance Network, and reports of rotavirus detection from a sentinel system of laboratories. At the state and local levels, surveillance efforts at sentinel hospitals or by review of hospital discharge databases can

be used to monitor the impact of the vaccine program. Special studies (e.g., case-control studies and retrospective cohort studies) will be used to measure the effectiveness of rotavirus vaccine under routine use in the United States. CDC has established a national strain surveillance system of sentinel laboratories to monitor circulating rotavirus strains before and after the introduction of rotavirus vaccine. This system is designed to detect new or unusual strains causing gastroenteritis that might not be prevented effectively by vaccination, which might affect the success of the vaccination program.

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Rubella

The name rubella is derived from Latin, meaning "little red." Rubella was initially considered to be a variant of measles or scarlet fever and was called "third disease." It was not until 1814 that it was first described as a separate disease in the German medical literature, hence the common name "German measles." In 1914, Hess postulated a viral etiology based on his work with monkeys. Hiro and Tosaka in 1938 confirmed the viral etiology by passing the disease to children using filtered nasal washings from persons with acute cases.

Following a widespread epidemic of rubella infection in 1940, Norman Gregg, an Australian ophthalmologist, reported in 1941 the occurrence of congenital cataracts among 78 infants born following maternal rubella infection in early pregnancy. This was the first published recognition of congenital rubella syndrome (CRS). Rubella virus was first isolated in 1962 by Parkman and Weller. The first rubella vaccines were licensed in 1969.

Rubella
- From Latin meaning "little red"
- Discovered in 18th century - thought to be variant of measles
- First described as distinct clinical entity in German literature
- Congenital rubella syndrome (CRS) described by Gregg in 1941

Rubella Virus

Rubella virus is classified as a togavirus, genus *Rubivirus*. It is most closely related to group A arboviruses, such as eastern and western equine encephalitis viruses. It is an enveloped RNA virus, with a single antigenic type that does not cross-react with other members of the togavirus group. Rubella virus is relatively unstable and is inactivated by lipid solvents, trypsin, formalin, ultraviolet light, low pH, heat, and amantadine.

Rubella Virus
- Togavirus
- RNA virus
- One antigenic type
- Rapidly inactivated by chemical agents, ultraviolet light, low pH, and heat

Pathogenesis

Following respiratory transmission of rubella virus, replication of the virus is thought to occur in the nasopharynx and regional lymph nodes. A viremia occurs 5 to 7 days after exposure with spread of the virus throughout the body. Transplacental infection of the fetus occurs during viremia. Fetal damage occurs through destruction of cells as well as mitotic arrest.

Rubella Pathogenesis
- Respiratory transmission of virus
- Replication in nasopharynx and regional lymph nodes
- Viremia 5-7 days after exposure with spread to tissues
- Placenta and fetus infected during viremia

Clinical Features

Acquired Rubella

The incubation period of rubella is 14 days, with a range of 12 to 23 days. Symptoms are often mild, and up to 50% of infections may be subclinical or inapparent. In children, rash is usually the first manifestation and a prodrome is rare. In older children and adults, there is often a 1 to 5 day prodrome with low-grade fever, malaise, lymphadenopathy, and upper respiratory symptoms preceding the rash. The rash of rubella is maculopapular and occurs 14 to 17 days after exposure. The rash usually occurs initially on the

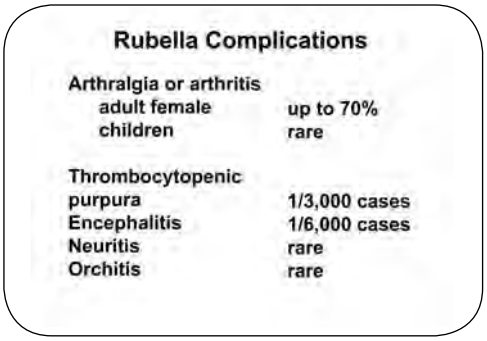
Rubella Clinical Features
- Incubation period 14 days (range 12-23 days)
- Prodrome of low-grade fever
- Maculopapular rash 14-17 days after exposure
- Lymphadenopathy in second week

face and then progresses from head to foot. It lasts about 3 days and is occasionally pruritic. The rash is fainter than measles rash and does not coalesce. The rash is often more prominent after a hot shower or bath. Lymphadenopathy may begin a week before the rash and last several weeks. Postauricular, posterior cervical, and suboccipital nodes are commonly involved.

Arthralgia and arthritis occur so frequently in adults that they are considered by many to be an integral part of the illness rather than a complication. Other symptoms of rubella include conjunctivitis, testalgia, or orchitis. Forschheimer spots may be noted on the soft palate but are not diagnostic for rubella.

Complications

Complications of rubella are not common, but they generally occur more often in adults than in children.



Arthralgia or arthritis may occur in up to 70% of adult women who contract rubella, but it is rare in children and adult males. Fingers, wrists, and knees are often affected. Joint symptoms tend to occur about the same time or shortly after appearance of the rash and may last for up to 1 month; chronic arthritis is rare.

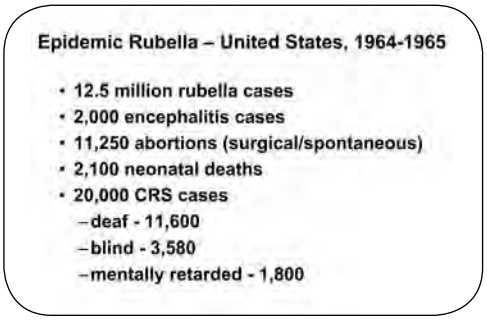
Encephalitis occurs in one in 6,000 cases, more frequently in adults (especially in females) than in children. Mortality estimates vary from 0 to 50%.

Hemorrhagic manifestations occur in approximately one per 3,000 cases, occurring more often in children than in adults. These manifestations may be secondary to low platelets and vascular damage, with thrombocytopenic purpura being the most common manifestation. Gastrointestinal, cerebral, or intrarenal hemorrhage may occur. Effects may last from days to months, and most patients recover.

Additional complications include orchitis, neuritis, and a rare late syndrome of progressive panencephalitis.

Congenital Rubella Syndrome

Prevention of CRS is the main objective of rubella vaccination programs in the United States.



A rubella epidemic in the United States in 1964–1965 resulted in 12.5 million cases of rubella infection and about 20,000 newborns with CRS. The estimated cost of the epidemic was $840 million. This does not include the emotional toll on the families involved.

Infection with rubella virus is most severe in early gestation. The virus may affect all organs and cause a variety

of congenital defects. Infection may lead to fetal death, spontaneous abortion, or premature delivery. The severity of the effects of rubella virus on the fetus depends largely on the time of gestation at which infection occurs. As many as 85% of infants infected in the first trimester of pregnancy will be found to be affected if followed after birth. While fetal infection may occur throughout pregnancy, defects are rare when infection occurs after the 20th week of gestation. The overall risk of defects during the third trimester is probably no greater than that associated with uncomplicated pregnancies.

Congenital Rubella Syndrome

- Infection may affect all organs
- May lead to fetal death or premature delivery
- Severity of damage to fetus depends on gestational age
- Up to 85% of infants affected if infected during first trimester

Congenital infection with rubella virus can affect virtually all organ systems. Deafness is the most common and often the sole manifestation of congenital rubella infection, especially after the fourth month of gestation. Eye defects, including cataracts, glaucoma, retinopathy, and microphthalmia may occur. Cardiac defects such as patent ductus arteriosus, ventricular septal defect, pulmonic stenosis, and coarctation of the aorta are possible. Neurologic abnormalities, including microcephaly and mental retardation, and other abnormalities, including bone lesions, splenomegaly, hepatitis, and thrombocytopenia with purpura may occur.

Congenital Rubella Syndrome

- Deafness
- Cataracts
- Heart defects
- Microcephaly
- Mental retardation
- Bone alterations
- Liver and spleen damage

Manifestations of CRS may be delayed from 2 to 4 years. Diabetes mellitus appearing in later childhood occurs frequently in children with CRS. In addition, progressive encephalopathy resembling subacute sclerosing panencephalitis has been observed in some older children with CRS. Children with CRS have a higher than expected incidence of autism.

Infants with CRS may have low titers by hemagglutination inhibition (HI) but may have high titers of neutralizing antibody that may persist for years. Reinfection may occur. Impaired cell-mediated immunity has been demonstrated in some children with CRS.

Laboratory Diagnosis

Many rash illnesses can mimic rubella infection, and as many as 50% of rubella infections may be subclinical. The only reliable evidence of acute rubella infection is a positive viral culture for rubella or detection of rubella virus by polymerase chain reaction, the presence of rubella-specific IgM antibody, or demonstration of a significant rise in IgG antibody from paired acute- and convalescent-phase sera.

Rubella Laboratory Diagnosis

- Isolation of rubella virus from clinical specimen (e.g., nasopharynx, urine)
- Positive serologic test for rubella IgM antibody
- Significant rise in rubella IgG by any standard serologic assay (e.g., enzyme immunoassay)

Rubella virus can be isolated from nasal, blood, throat, urine and cerebrospinal fluid specimens from rubella and CRS patients. Virus may be isolated from the pharynx 1 week before and until 2 weeks after rash onset. Although isolation of the virus is diagnostic of rubella infection, viral cultures are labor intensive, and therefore not done in many laboratories; they are generally not used for routine diagnosis of

rubella. Viral isolation is an extremely valuable epidemiologic tool and should be attempted for all suspected cases of rubella or CRS. Information about rubella virus isolation can be found on the CDC website at http://www.cdc.gov/ncidod/dvrd/revb/measles/surv_rubellavirus.htm.

Serology is the most common method of confirming the diagnosis of rubella. Acute rubella infection can be serologically confirmed by a significant rise in rubella antibody titer in acute- and convalescent-phase serum specimens or by the presence of serum rubella IgM. Serum should be collected as early as possible (within 7–10 days) after onset of illness, and again 14–21 days (minimum of 7) days later.

False-positive serum rubella IgM tests have occurred in persons with parvovirus infections, with a positive heterophile test for infectious mononucleosis, or with a positive rheumatoid factor.

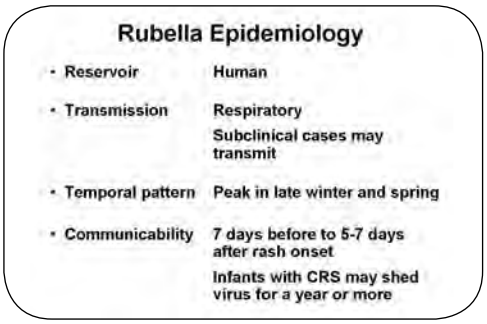
The serologic tests available for laboratory confirmation of rubella infections vary among laboratories. The state health department can provide guidance on available laboratory services and preferred tests.

Enzyme-linked immunosorbent assay (ELISA). ELISA is sensitive, widely available, and relatively easy to perform. It can also be modified to measure IgM antibodies. Most of the diagnostic testing done for rubella antibodies uses some variation of ELISA.

Epidemiology

Occurrence

Rubella occurs worldwide.



Reservoir

Rubella is a human disease. There is no known animal reservoir. Although infants with CRS may shed rubella virus for an extended period, a true carrier state has not been described.

Transmission

Rubella is spread from person to person via airborne transmission or droplets shed from the respiratory secretions of infected persons. There is no evidence of insect transmission.

Rubella may be transmitted by persons with subclinical or asymptomatic cases (up to 50% of all rubella virus infections).

Temporal Pattern

In temperate areas, incidence is usually highest in late winter and early spring.

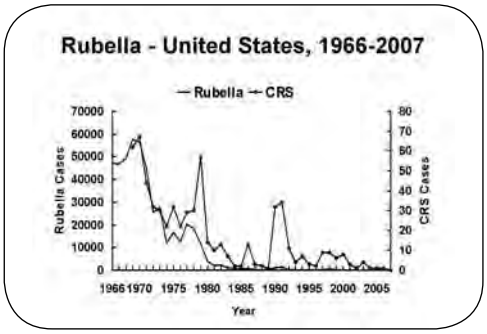
Communicability

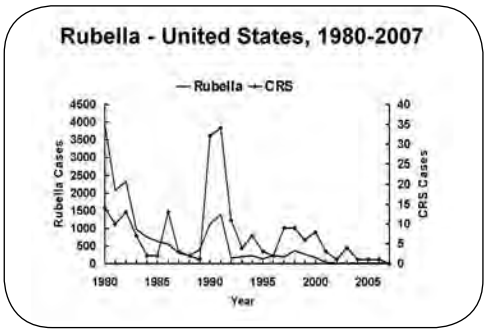
Rubella is only moderately contagious. The disease is most contagious when the rash first appears, but virus may be shed from 7 days before to 5–7 days or more after rash onset.

Infants with CRS shed large quantities of virus from body secretions for up to 1 year and can therefore transmit rubella to persons caring for them who are susceptible to the disease.

Secular Trends in the United States

Rubella and congenital rubella syndrome became nationally notifiable diseases in 1966. The largest annual total of cases of rubella in the United States was in 1969, when 57,686 cases were reported (58 cases per 100,000 population). Following vaccine licensure in 1969, rubella incidence declined rapidly. By 1983, fewer than 1,000 cases per year were reported (less than 0.5 cases per 100,000 population). A moderate resurgence of rubella occurred in 1990–1991, primarily due to outbreaks in California (1990) and among the Amish in Pennsylvania (1991). In 2003, a record low annual total of seven cases was reported. In October 2004, CDC convened an independent expert panel to review available rubella and CRS data. After a careful review, the panel unanimously agreed that rubella was no longer endemic in the United States.





Until recently, there was no predominant age group for rubella cases. From 1982 through 1992, approximately 30% of cases occurred in each of three age groups: younger than 5, 5–14, and 15–39 years. Adults 40 years of age and older typically accounted for less than 10% of cases. However, since 1993, persons 15–39 years of age have accounted for more than half the cases. In 2003, this age group accounted for 71% of all reported cases.

Most reported rubella in the United States since the mid-1990s has occurred among Hispanic young adults who were born in areas where rubella vaccine is routinely not given.

CRS surveillance is maintained through the National Congenital Rubella Registry, which is managed by the National Center for Immunization and Respiratory Diseases. The largest annual total of reported CRS cases to the registry was in 1970 (67 cases). An average of 5–6 CRS cases have been reported annually since 1980. Although reported rubella activity has consistently and significantly decreased since vaccine has been used in the United States, the incidence of CRS has paralleled the decrease in rubella cases only since the mid-1970s. The decline in CRS since the mid-1970s was due to an increased effort to vaccinate

Rubella and CRS in the United States

- Most reported rubella in the U.S. since the mid-1990s has occurred among foreign-born Hispanic adult
- Majority of CRS since 1997 occurred in children of unvaccinated women born to Hispanic women, many born in Latin America

susceptible adolescents and young adults, especially women. Rubella outbreaks are almost always followed by an increase in CRS.

Rubella outbreaks in California and Pennsylvania in 1990–1991 resulted in 25 cases of CRS in 1990 and 33 cases in 1991. Two CRS cases were reported in 2001, and in 2004, no cases were reported. Since 1997, the mothers of the majority of infants with CRS were Hispanic women, many of whom were born in Latin American or Caribbean countries where rubella vaccine is routinely not used or has only recently begun to be used.

Classification of Rubella Cases

Rubella Case Definition

- Acute onset of generalized maculopapular rash, and
- Temperature of >99°F (37.2 °C), if measured, and
- Arthralgia or arthritis, lymphadenopathy, or conjunctivitis

Clinical Case Definition of Acquired Rubella

A clinical case of rubella is defined as an illness with all of the following characteristics: 1) acute onset of generalized maculopapular rash; 2) a temperature higher than 99°F (37.2°C), if measured; and 3) arthralgia or arthritis, lymphadenopathy, or conjunctivitis. Cases meeting the measles case definition are excluded. Also excluded are cases with serology compatible with recent measles virus infection.

Case Classification of Acquired Rubella

A suspected case is any generalized rash illness of acute onset. A probable case meets the clinical case definition, has noncontributory or no serologic or virologic test results, and is not epidemiologically linked to a laboratory-confirmed case. A confirmed case is laboratory confirmed or meets the clinical case definition and is epidemiologically linked to a laboratory-confirmed case.

Clinical Case Definition of Congenital Rubella Syndrome

The clinical case definition of CRS is an illness, usually manifesting in infancy, resulting from rubella infection in utero and characterized by symptoms from the following categories:

A. Cataracts, congenital glaucoma, congenital heart disease (most commonly patent ductus arteriosus or peripheral pulmonary artery stenosis), loss of hearing, pigmentary retinopathy

B. Purpura, hepatosplenomegaly, jaundice, microcephaly, developmental delay, meningoencephalitis, radiolucent bone disease

Case Classification of Congenital Rubella Syndrome

An infection-only case is one with laboratory evidence of infection but without any clinical symptoms or signs. A suspected case has some compatible clinical findings, but does not meet the criteria for a probable case. A probable case is one that is not laboratory confirmed, has any two complications listed in category A above or one complication from category A and one from B, and lacks evidence of any other etiology. A confirmed case is a clinically consistent case that is laboratory confirmed. In probable cases, either or both of the eye-related findings (cataracts and congenital glaucoma) count as a single complication. In cases classified as infection only, if any compatible signs or symptoms (e.g., hearing loss) are identified later, the case is reclassified as confirmed.

Rubella Vaccine

Three rubella vaccines were licensed in the United States in 1969: HPV-77:DE-5 (duck embryo), HPV-77:DK-12 (dog kidney), and GMK-3:RK53 Cendevax (rabbit kidney) strains. HPV-77:DK-12 was later removed from the market because there was a higher rate of joint complaints following vaccination with this strain. In 1979, the RA 27/3 (human diploid fibroblast) strain (Meruvax-II, Merck) was licensed and all other strains were discontinued.

Rubella Vaccine

Vaccine	Trade Name	Licensure
HPV-77:DE5	Meruvax	1969
HPV-77:DK12	Rubelogen	1969
GMK-3:RK53	Cendevax	1969
RA 27/3*	Meruvax II	1979

*Only vaccine currently licensed in U.S.

Characteristics

The RA 27/3 rubella vaccine is a live attenuated virus. It was first isolated in 1965 at the Wistar Institute from a rubella-infected aborted fetus. The virus was attenuated by 25–30 passages in tissue culture, using human diploid fibroblasts. It does not contain duck, chicken or egg protein.

Vaccine virus is not communicable except in the setting of breastfeeding (see Contraindications, below), even though virus may be cultured from the nasopharynx of vaccinees.

Rubella Vaccine

- Composition: Live virus (RA 27/3 strain)
- Efficacy: 95% (Range, 90%-97%)
- Duration of Immunity: Lifelong
- Schedule: At least 1 dose
- Should be administered with measles and mumps as MMR or with measles, mumps and varicella as MMRV

Rubella vaccine is available combined with measles and mumps vaccines as MMR, or combined with mumps, measles, and varicella vaccine as MMRV (ProQuad). The Advisory Committee on Immunization Practices (ACIP) recommends that combined measles-mumps-rubella vaccine (MMR) be used when any of the individual components is indicated. Use of single-antigen rubella vaccine is not recommended.

MMR and MMRV are supplied as a lyophylized (freeze-dried) powder and are reconstituted with sterile, preservative-free water. The vaccines contains a small amount of human albumin, neomycin, sorbitol, and gelatin.

Immunogenicity and Vaccine Efficacy

RA 27/3 rubella vaccine is safe and more immunogenic than rubella vaccines used previously. In clinical trials, 95% or more of vaccinees aged 12 months and older developed serologic evidence of rubella immunity after a single dose. More than 90% of vaccinated persons have protection against both clinical rubella and viremia for at least 15 years. Follow-up studies indicate that one dose of vaccine confers long-term, probably lifelong, protection. Seroconversion rates are similar for single-antigen rubella vaccine, MMR, and MMRV.

Several reports indicate that viremic reinfection following exposure may occur in vaccinated persons who have low levels of detectable antibody. The frequency and consequences of this phenomenon are unknown, but it is believed to be uncommon. Rarely, clinical reinfection and fetal infection have been reported among women with vaccine-induced immunity. Rare cases of CRS have occurred among infants born to women who had documented serologic evidence of rubella immunity before they became pregnant.

Vaccination Schedule and Use

Rubella Vaccine (MMR) Indications

- All infants 12 months of age and older
- Susceptible adolescents and adults without documented evidence of rubella immunity
- Emphasis on nonpregnant women of childbearing age, particularly those born outside the U.S.

At least one dose of rubella-containing vaccine, as combination MMR (or MMRV) vaccine, is routinely recommended for all children 12 months of age or older. All persons born during or after 1957 should have documentation of at least one dose of MMR. The first dose of MMR should be given on or after the first birthday. Any dose of rubella-containing vaccine given before 12 months of age should not be counted as part of the series. Children vaccinated with rubella-containing vaccine before 12 months of age should be revaccinated when the child is at least 12 months of age.

A second dose of MMR is recommended to produce immunity to measles and mumps in those who failed to respond to the first dose. Data indicate that almost all persons who do not respond to the measles component of the first dose will respond to a second dose of MMR. Few data on the immune response to the rubella and mumps components of a second dose of MMR are available. However, most persons who do not respond to the rubella or mumps component of the first MMR dose would be expected to respond to the second dose. The second dose is not generally considered a booster dose because a primary immune response to the first dose provides long-term protection. Although a second dose of vaccine may increase antibody titers in some persons who responded to the first dose, available data indicate that these increased antibody titers are not sustained. The combined

MMR vaccine is recommended for both doses to ensure immunity to all three viruses.

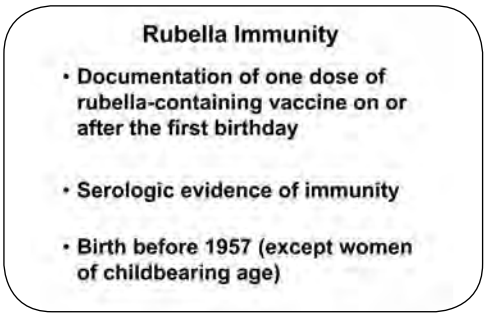
The second dose of MMR vaccine should routinely be given at age 4 through 6 years, before a child enters kindergarten or first grade. The recommended health visit at age 11 or 12 years can serve as a catch-up opportunity to verify vaccination status and administer MMR vaccine to those children who have not yet received two doses of MMR (with the first dose administered no earlier than the first birthday). The second dose of MMR may be administered as soon as 1 month (i.e., minimum of 28 days) after the first dose. The minimum interval between doses of MMRV is 3 months.

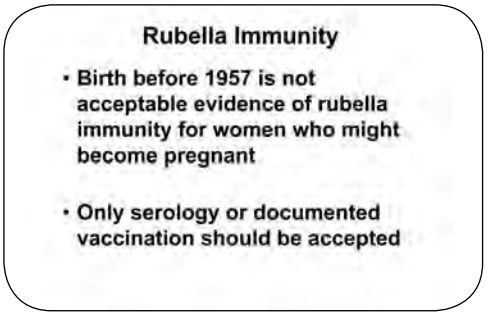
All older children not previously immunized should receive at least one dose of rubella vaccine as MMR or MMRV if 12 years of age or younger.

Adults born in 1957 or later who do not have a medical contraindication should receive at least one dose of MMR vaccine unless they have documentation of vaccination with at least one dose of measles-, mumps-, and rubella-containing vaccine or other acceptable evidence of immunity to these three diseases. Some adults at high risk of measles and mumps exposure may require a second dose. This second dose should be administered as combined MMR vaccine (see Measles chapter for details). Efforts should be made to identify and vaccinate susceptible adolescents and adults, particularly women of childbearing age who are not pregnant. Particular emphasis should be placed on vaccinating both males and females in colleges, places of employment, and healthcare settings.

Only doses of vaccine with written documentation of the date of receipt should be accepted as valid. Self-reported doses or a parental report of vaccination is not considered adequate documentation. A healthcare provider should not provide an immunization record for a patient unless that healthcare provider has administered the vaccine or has seen a record that documents vaccination. Persons who lack adequate documentation of vaccination or other acceptable evidence of immunity should be vaccinated. Vaccination status and receipt of all vaccinations should be documented in the patient's permanent medical record and in a vaccination record held by the individual.

MMRV is approved by the Food and Drug Administration for children 12 months through 12 years of age (that is, until the 13th birthday). MMRV should not be administered to persons 13 years or older.





Rubella Immunity

Persons generally can be considered immune to rubella if they have documentation of vaccination with at least one dose of MMR (or MMRV) or other live rubella-containing vaccine administered on or after their first birthday, have serologic evidence of rubella immunity, or were born before 1957. Persons who have an "equivocal" serologic test result should be considered rubella-susceptible. Although only one dose of rubella-containing vaccine is required as acceptable evidence of immunity to rubella, children should receive two doses of MMR vaccine according to the routine childhood vaccination schedule.

Birth before 1957 provides only presumptive evidence of rubella immunity; it does not guarantee that a person is immune to rubella. Because rubella can occur in some unvaccinated persons born before 1957 and because congenital rubella and congenital rubella syndrome can occur in the offspring of women infected with rubella during pregnancy, birth before 1957 is not acceptable evidence of rubella immunity for women who might become pregnant. Only a positive serologic test for rubella antibody or documentation of appropriate vaccination should be accepted for women who may become pregnant.

Healthcare personnel born before 1957 also should not be presumed to be immune. Medical facilities should consider recommending at least one dose of MMR vaccine to unvaccinated healthcare personnel born before 1957 who do not have laboratory evidence of rubella immunity. Rubella vaccination or laboratory evidence of rubella immunity is particularly important for healthcare personnel who could become pregnant, including those born before 1957. This recommendation is based on serologic studies which indicate that among hospital personnel born before 1957, 5% to 9% had no detectable measles antibody.

Clinical diagnosis of rubella is unreliable and should not be considered in assessing immune status. Because many rash illnesses may mimic rubella infection and many rubella infections are unrecognized, the only reliable evidence of previous rubella infection is the presence of serum rubella IgG antibody. Laboratories that regularly perform antibody testing are generally the most reliable because their reagents and procedures are strictly standardized.

Occasionally, a person with a history of documented rubella vaccination is found to have a negative serum IgG by ELISA. Such persons may be given a dose of MMR vaccine and do not need to be retested for serologic evidence of rubella immunity.

Serologic screening need not be done before vaccinating for measles and rubella unless the medical facility considers it cost-effective. Serologic testing is appropriate only if tracking systems are used to ensure that tested persons who are identified as susceptible are subsequently vaccinated in a timely manner. If the return and timely vaccination of those screened cannot be assured, vaccination should be done without prior testing. Serologic testing for immunity to measles and rubella is not necessary for persons documented to be appropriately vaccinated or who have other acceptable evidence of immunity.

Neither rubella vaccine nor immune globulin is effective for postexposure prophylaxis of rubella. Vaccination after exposure is not harmful and may possibly avert later disease.

Contraindications and Precautions to Vaccination

Persons who have experienced a severe allergic reaction (anaphylaxis) to a vaccine compnent or following a prior dose of rubella vaccine should generally not be vaccinated with MMR.

MMR Vaccine
Contraindications and Precautions

- Severe allergic reaction to vaccine component or following a prior dose
- Pregnancy
- Immunosuppression
- Moderate or severe acute illness
- Recent blood product

Women known to be pregnant or attempting to become pregnant should not receive rubella vaccine. Although there is no evidence that rubella vaccine virus causes fetal damage, pregnancy should be avoided for 4 weeks (28 days) after rubella or MMR vaccination.

Persons with immunodeficiency or immunosuppression, resulting from leukemia, lymphoma, generalized malignancy, immune deficiency disease, or immunosuppressive therapy should not be vaccinated. However, treatment with low-dose (less than 2 mg/kg/day), alternate-day, topical, or aerosolized steroid preparations is not a contraindication to rubella vaccination. Persons whose immunosuppressive therapy with steroids has been discontinued for 1 month (3 months for chemotherapy) may be vaccinated. Rubella vaccine should be considered for persons with asymptomatic or mildly symptomatic HIV infection.

Persons with moderate or severe acute illness should not be vaccinated until the illness has improved. Minor illness (e.g., otitis media, mild upper respiratory infections), concurrent antibiotic therapy, and exposure or recovery from other illnesses are not contraindications to rubella vaccination.

Receipt of antibody-containing blood products (e.g., immune globulin, whole blood or packed red blood cells, intravenous immune globulin) may interfere with seroconversion to rubella vaccine. Vaccine should be given 2 weeks before, or deferred for at least 3 months following

administration of an antibody-containing blood product. If rubella vaccine is given as combined MMR, a longer delay may be necessary before vaccination. For more information, see Chapter 2, General Recommendations on Immunization.

Previous administration of human anti-Rho(D) immune globulin (RhoGam) does not generally interfere with an immune response to rubella vaccine and is not a contraindication to postpartum vaccination. However, women who have received anti-Rho immune globulin should be serologically tested 6–8 weeks after vaccination to ensure that seroconversion has occurred.

Although vaccine virus may be isolated from the pharynx, vaccinees do not transmit rubella to others, except occasionally in the case of the vaccinated breastfeeding woman. In this situation, the infant may be infected, presumably through breast milk, and may develop a mild rash illness, but serious effects have not been reported. Infants infected through breastfeeding have been shown to respond normally to rubella vaccination at 12–15 months of age. Breastfeeding is not a contraindication to rubella vaccination and does not alter rubella vaccination recommendations.

Adverse Reactions Following Vaccination

Rubella vaccine is very safe. Most adverse reactions reported following MMR vaccination (such as fever and rash) are attributable to the measles component. The most common complaints following rubella vaccination are fever, lymphadenopathy, and arthralgia. These adverse reactions only occur in susceptible persons and are more common in adults, especially in women.

MMR Adverse Reactions

• Fever	5%-15%
• Rash	5%
• Joint symptoms	25%
• Thrombocytopenia	<1/30,000 doses
• Parotitis	rare
• Deafness	rare
• Encephalopathy	<1/1,000,000 doses

Rubella Vaccine Arthropathy

- Acute arthralgia in about 25% of vaccinated, susceptible adult women
- Acute arthritis-like signs and symptoms occurs in about 10% of recipients
- Rare reports of chronic or persistent symptoms
- Population-based studies have not confirmed an association with rubella vaccine

Joint symptoms, such as arthralgia (joint pain) and arthritis (joint redness and/or swelling), are associated with the rubella component of MMR. Arthralgia and transient arthritis occur more frequently in susceptible adults than in children and more frequently in susceptible women than in men. Acute arthralgia or arthritis is rare following vaccination of children with RA 27/3 vaccine. By contrast, approximately 25% of susceptible postpubertal females develop acute arthralgia following RA 27/3 vaccination, and approximately 10% have been reported to have acute arthritis-like signs and symptoms. Rarely, transient peripheral neuritic complaints, such as paresthesias and pain in the arms and legs, have been reported.

When acute joint symptoms occur, or when pain or paresthesias not associated with joints occur, the symptoms generally begin 1–3 weeks after vaccination, persist for 1 day to 3 weeks, and rarely recur. Adults with acute joint symptoms following rubella vaccination rarely have had to

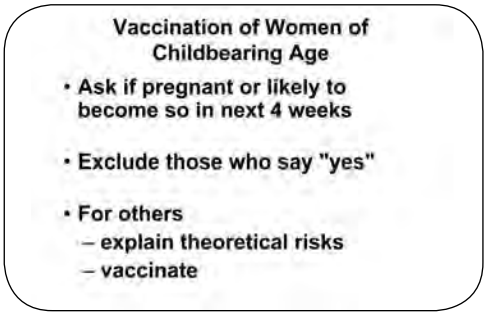
disrupt work activities.

Data from studies in the United States and experience from other countries using the RA 27/3 strain rubella vaccine have not supported an association between the vaccine and chronic arthritis. One study among 958 seronegative immunized and 932 seronegative unimmunized women aged 15–39 years found no association between rubella vaccination and development of recurrent joint symptoms, neuropathy, or collagen disease.

The ACIP continues to recommend the vaccination of all adult women who do not have evidence of rubella immunity.

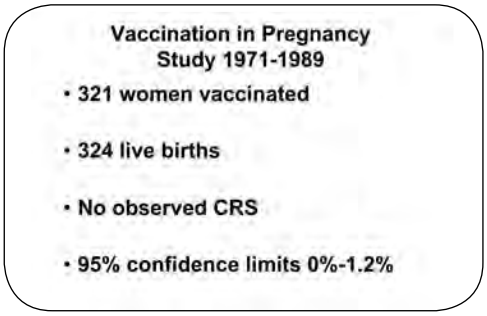
Rubella Vaccination of Women of Childbearing Age

Women who are pregnant or who intend to become pregnant within 4 weeks should not receive rubella vaccine. ACIP recommends that vaccine providers ask a woman if she is pregnant or likely to become pregnant in the next 4 weeks. Those who are pregnant or intend to become pregnant should not be vaccinated. All other women should be vaccinated after being informed of the theoretical risks of vaccination during pregnancy and the importance of not becoming pregnant during the 4 weeks following vaccination. ACIP does not recommend routine pregnancy screening of women before rubella vaccination.



If a pregnant woman is inadvertently vaccinated or if she becomes pregnant within 4 weeks after vaccination, she should be counseled about the concern for the fetus (see below), but MMR vaccination during pregnancy should not ordinarily be a reason to consider termination of the pregnancy.

When rubella vaccine was licensed, concern existed about women being inadvertently vaccinated while they were pregnant or shortly before conception. This concern came from the known teratogenicity of the wild-virus strain. To determine whether CRS would occur in infants of such mothers. CDC maintained a registry from 1971 to 1989 of women vaccinated during pregnancy. This was called the Vaccine in Pregnancy (VIP) Registry.



Although subclinical fetal infection has been detected serologically in approximately 1%–2% of infants born to susceptible vaccinees, regardless of the vaccine strain, the data collected by CDC in the VIP Registry showed no evidence of CRS occurring in offspring of the 321 susceptible women who received rubella vaccine and who continued pregnancy to term. The observed risk of vaccine-induced malformation was 0%, with a maximum theoretical risk of

1.6%, based on 95% confidence limits (1.2% for all types of rubella vaccine). Since the risk of the vaccine to the fetus appears to be extremely low, if it exists at all, routine termination of pregnancy is not recommended. Individual counseling for these women is recommended. As of April 30, 1989, CDC discontinued the VIP registry.

The ACIP continues to state that because of the small theoretical risk to the fetus of a vaccinated woman, pregnant women should not be vaccinated.

Vaccine Storage and Handling

MMR and MMRV vaccines must be shipped with refrigerant to maintain a temperature of 50°F (10°C) or less at all times. Vaccine must be refrigerated immediately on arrival and protected from light at all times. The vaccine must be stored at refrigerator temperature (35°–46°F [2°–8°C]), but may be frozen. Diluent may be stored at refrigerator temperature or at room temperature. MMRV must be shipped to maintain a temperature of -4°F (-20°C) or colder at all times. MMRV must be stored at an average temperature of 5°F (-15°C) or colder at all times.

After reconstitution, MMR vaccines must be stored at refrigerator temperature and protected from light. Reconstituted vaccine should be used immediately. If reconstituted vaccine is not used within 8 hours, it must be discarded. MMRV must be administered within 30 minutes of reconstitution.

Strategies to Decrease Rubella and CRS

Vaccination of Susceptible Postpubertal Females

Elimination of indigenous rubella and CRS can be maintained by continuing efforts to vaccinate susceptible adolescents and young adults of childbearing age, particularly those born outside the United States. These efforts should include vaccinating in family planning clinics, sexually transmitted disease (STD) clinics, and as part of routine gynecologic care; maximizing use of premarital serology results; emphasizing immunization for college students; vaccinating women postpartum and postabortion; immunizing prison staff and, when possible, prison inmates, especially women inmates; offering vaccination to at-risk women through the special supplemental program for Women, Infants and Children (WIC); and implementing vaccination programs in the workplace, particularly those employing persons born outside the United States.

Hospital Rubella Programs

Emphasis should be placed on vaccinating susceptible hospital personnel, both male and female (e.g., volunteers, trainees, nurses, physicians.) Ideally, all hospital employees should be immune. It is important to note that screening programs alone are not adequate. Vaccination of susceptible staff must follow.

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Rubella

Tetanus

Tetanus is an acute, often fatal, disease caused by an exotoxin produced by the bacterium *Clostridium tetani*. It is characterized by generalized rigidity and convulsive spasms of skeletal muscles. The muscle stiffness usually involves the jaw (lockjaw) and neck and then becomes generalized.

Although records from antiquity (5th century BCE) contain clinical descriptions of tetanus, it was Carle and Rattone in 1884 who first produced tetanus in animals by injecting them with pus from a fatal human tetanus case. During the same year, Nicolaier produced tetanus in animals by injecting them with samples of soil. In 1889, Kitasato isolated the organism from a human victim, showed that it produced disease when injected into animals, and reported that the toxin could be neutralized by specific antibodies. In 1897, Nocard demonstrated the protective effect of passively transferred antitoxin, and passive immunization in humans was used for treatment and prophylaxis during World War I. Tetanus toxoid was developed by Descombey in 1924. It was first widely used during World War II.

Tetanus

- First described by Hippocrates
- Etiology discovered in 1884 by Carle and Rattone
- Passive immunization used for treatment and prophylaxis during World War I
- Tetanus toxoid first widely used during World War II

Clostridium tetani

C. tetani is a slender, gram-positive, anaerobic rod that may develop a terminal spore, giving it a drumstick appearance. The organism is sensitive to heat and cannot survive in the presence of oxygen. The spores, in contrast, are very resistant to heat and the usual antiseptics. They can survive autoclaving at 249.8°F (121°C) for 10–15 minutes. The spores are also relatively resistant to phenol and other chemical agents.

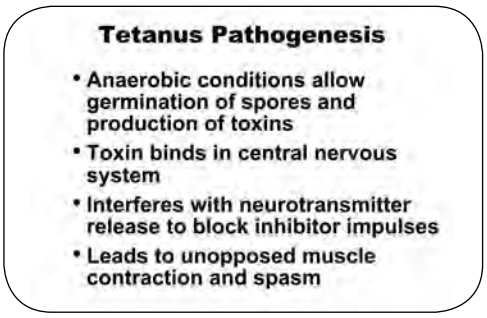
The spores are widely distributed in soil and in the intestines and feces of horses, sheep, cattle, dogs, cats, rats, guinea pigs, and chickens. Manure-treated soil may contain large numbers of spores. In agricultural areas, a significant number of human adults may harbor the organism. The spores can also be found on skin surfaces and in contaminated heroin.

C. tetani produces two exotoxins, tetanolysin and tetanospasmin. The function of tetanolysin is not known with certainty. Tetanospasmin is a neurotoxin and causes the clinical manifestations of tetanus. On the basis of weight, tetanospasmin is one of the most potent toxins known. The estimated minimum human lethal dose is 2.5 nanograms per kilogram of body weight (a nanogram is one billionth of a gram), or 175 nanograms for a 70-kg (154lb) human.

Clostridium tetani

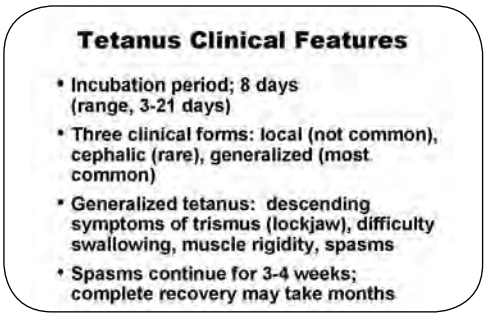
- Anaerobic gram-positive, spore-forming bacteria
- Spores found in soil, animal feces; may persist for months to years
- Multiple toxins produced with growth of bacteria
- Tetanospasmin estimated human lethal dose = 2.5 ng/kg

Tetanus



Pathogenesis

C. tetani usually enters the body through a wound. In the presence of anaerobic (low oxygen) conditions, the spores germinate. Toxins are produced and disseminated via blood and lymphatics. Toxins act at several sites within the central nervous system, including peripheral motor end plates, spinal cord, and brain, and in the sympathetic nervous system. The typical clinical manifestations of tetanus are caused when tetanus toxin interferes with release of neurotransmitters, blocking inhibitor impulses. This leads to unopposed muscle contraction and spasm. Seizures may occur, and the autonomic nervous system may also be affected.



Clinical Features

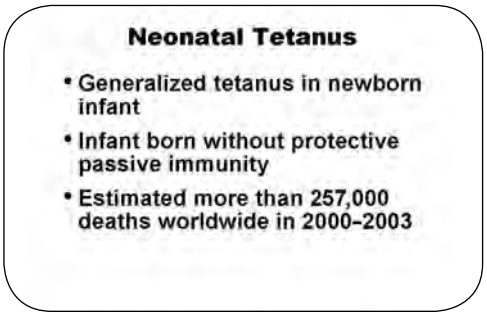
The incubation period ranges from 3 to 21 days, usually about 8 days. In general the further the injury site is from the central nervous system, the longer the incubation period. The shorter the incubation period, the higher the chance of death. In neonatal tetanus, symptoms usually appear from 4 to 14 days after birth, averaging about 7 days.

On the basis of clinical findings, three different forms of tetanus have been described.

Local tetanus is an uncommon form of the disease, in which patients have persistent contraction of muscles in the same anatomic area as the injury. These contractions may persist for many weeks before gradually subsiding. Local tetanus may precede the onset of generalized tetanus but is generally milder. Only about 1% of cases are fatal.

Cephalic tetanus is a rare form of the disease, occasionally occurring with otitis media (ear infections) in which *C. tetani* is present in the flora of the middle ear, or following injuries to the head. There is involvement of the cranial nerves, especially in the facial area.

The most common type (about 80%) of reported tetanus is generalized tetanus. The disease usually presents with a descending pattern. The first sign is trismus or lockjaw, followed by stiffness of the neck, difficulty in swallowing, and rigidity of abdominal muscles. Other symptoms include elevated temperature, sweating, elevated blood pressure, and episodic rapid heart rate. Spasms may occur frequently and last for several minutes. Spasms continue for 3–4 weeks. Complete recovery may take months.



Neonatal tetanus is a form of generalized tetanus that occurs in newborn infants. Neonatal tetanus occurs in infants born without protective passive immunity, because the mother is not immune. It usually occurs through infection of the unhealed umbilical stump, particularly when the

stump is cut with an unsterile instrument. Neonatal tetanus is common in some developing countries (estimated more than 257,000 annual deaths worldwide in 2000-2003), but very rare in the United States.

Complications

Laryngospasm (spasm of the vocal cords) and/or spasm of the muscles of respiration leads to interference with breathing. Fractures of the spine or long bones may result from sustained contractions and convulsions. Hyperactivity of the autonomic nervous system may lead to hypertension and/or an abnormal heart rhythm.

Nosocomial infections are common because of prolonged hospitalization. Secondary infections may include sepsis from indwelling catheters, hospital-acquired pneumonias, and decubitus ulcers. Pulmonary embolism is particularly a problem in drug users and elderly patients. Aspiration pneumonia is a common late complication of tetanus, found in 50%–70% of autopsied cases. In recent years, tetanus has been fatal in approximately 11% of reported cases. Cases most likely to be fatal are those occurring in persons 60 years of age and older (18%) and unvaccinated persons (22%). In about 20% of tetanus deaths, no obvious pathology is identified and death is attributed to the direct effects of tetanus toxin.

Tetanus Complications

- Laryngospasm
- Fractures
- Hypertension
- Nosocomial infections
- Pulmonary embolism
- Aspiration pneumonia
- Death

Laboratory Diagnosis

There are no laboratory findings characteristic of tetanus. The diagnosis is entirely clinical and does not depend upon bacteriologic confirmation. *C. tetani* is recovered from the wound in only 30% of cases and can be isolated from patients who do not have tetanus. Laboratory identification of the organism depends most importantly on the demonstration of toxin production in mice.

Medical Management

All wounds should be cleaned. Necrotic tissue and foreign material should be removed. If tetanic spasms are occurring, supportive therapy and maintenance of an adequate airway are critical.

Tetanus immune globulin (TIG) is recommended for persons with tetanus. TIG can only help remove unbound tetanus toxin. It cannot affect toxin bound to nerve endings. A single intramuscular dose of 3,000 to 5,000 units is generally recommended for children and adults, with part of the dose infiltrated around the wound if it can be identified. Intravenous immune globulin (IVIG) contains tetanus antitoxin and may be used if TIG is not available.

Tetanus

Tetanus Wound Management

Vaccination History	Clean, minor wounds: Td*	Clean, minor wounds: TIG	All other wounds: Td*	All other wounds: TIG
Unknown or less than 3 doses	Yes	No	Yes	Yes
3 or more doses	No+	No	No**	No

* Tdap may be substituted for Td if the person has not previously received Tdap and is 10 years or older
+ Yes, if more than 10 years since last dose
** Yes, if more than 5 years since last dose

Because of the extreme potency of the toxin, tetanus disease does not result in tetanus immunity. Active immunization with tetanus toxoid should begin or continue as soon as the person's condition has stabilized.

Wound Management

Antibiotic prophylaxis against tetanus is neither practical nor useful in managing wounds; proper immunization plays the more important role. The need for active immunization, with or without passive immunization, depends on the condition of the wound and the patient's immunization history (see *MMWR* 2006;55[RR-17] for details). Rarely have cases of tetanus occurred in persons with a documented primary series of tetanus toxoid.

Persons with wounds that are neither clean nor minor, and who have had 0–2 prior doses of tetanus toxoid or have an uncertain history of prior doses should receive TIG as well as Td or Tdap. This is because early doses of toxoid may not induce immunity, but only prime the immune system. The TIG provides temporary immunity by directly providing antitoxin. This ensures that protective levels of antitoxin are achieved even if an immune response has not yet occurred.

Epidemiology

Occurrence

Tetanus occurs worldwide but is most frequently encountered in densely populated regions in hot, damp climates with soil rich in organic matter.

Tetanus Epidemiology

• Reservoir	Soil and intestine of animals and humans
• Transmission	Contaminated wounds Tissue injury
• Temporal pattern	Peak in summer or wet season
• Communicability	Not contagious

Reservoir

Organisms are found primarily in the soil and intestinal tracts of animals and humans.

Mode of Transmission

Transmission is primarily by contaminated wounds (apparent and inapparent). The wound may be major or minor. In recent years, however, a higher proportion of patients had minor wounds, probably because severe wounds are more likely to be properly managed. Tetanus may follow elective surgery, burns, deep puncture wounds, crush wounds, otitis media (ear infections), dental infection, animal bites, abortion, and pregnancy.

Communicability

Tetanus is not contagious from person to person. It is the only vaccine-preventable disease that is infectious but not contagious.

Secular Trends in the United States

A marked decrease in mortality from tetanus occurred from the early 1900s to the late 1940s. In the late 1940s, tetanus toxoid was introduced into routine childhood immunization and tetanus became nationally notifiable. At that time, 500–600 cases (approximately 0.4 cases per 100,000 population) were reported per year.

After the 1940s, reported tetanus incidence rates declined steadily. Since the mid-1970s, 50–100 cases (~0.05 cases per 100,000) have been reported annually. From 2000 through 2007 an average of 31 cases were reported per year. The death-to-case ratio has declined from 30% to approximately 10% in recent years. An all-time low of 20 cases (0.01 cases per 100,000) was reported in 2003.

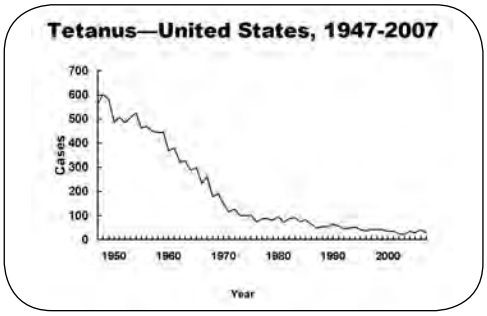
From 1980 through 2000, 70% of reported cases of tetanus were among persons 40 years of age or older. From 1980 through 1990, a median of 21% of reported cases were among persons younger than 40 years of age. The age distribution of reported cases shifted to a younger age group in the last half of the 1990s. Persons younger than 40 years accounted for 28% of cases during 1991–1995, increasing to 42% of cases during 1996–2000. This change in age distribution is a result of both an increase in cases in persons younger than 40 years and a decrease in cases in older people. The increase in cases among younger persons is related in part to an increased number of cases among young injection-drug users in California in the late 1990s.

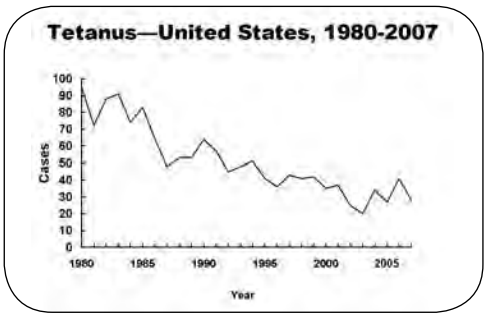
Almost all reported cases of tetanus are in persons who have either never been vaccinated, or who completed a primary series but have not had a booster in the preceding 10 years.

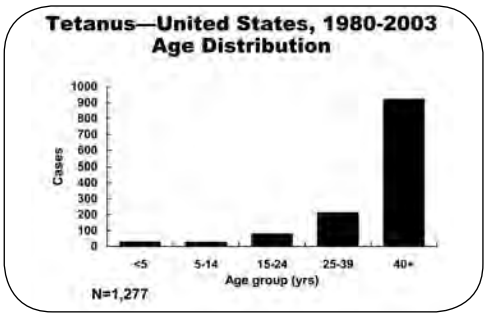
Heroin users, particularly persons who inject themselves subcutaneously, appear to be at high risk for tetanus. Quinine is used to dilute heroin and may support the growth of *C. tetani*.

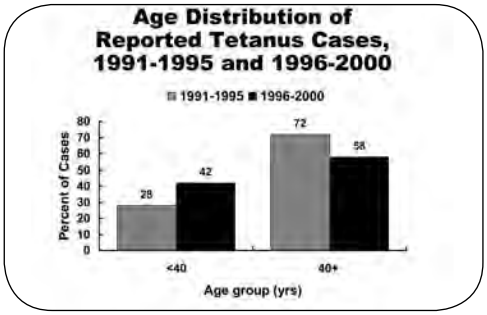
Neonatal tetanus is rare in the United States, with only two cases reported since 1989. Neither of the infants' mothers had ever received tetanus toxoid.

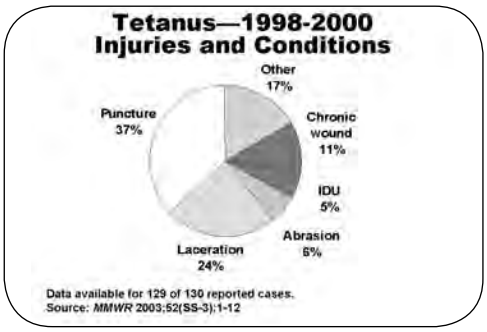
During 1998–2000 (the most recent years for which data are available), acute injuries or wounds preceded tetanus in 94 (73%) of the 129 cases for which information was available. Among the most frequent wound types were puncture wounds (50%), lacerations (33%), and abrasions (9%). The most common puncture wound was from stepping on a nail (15 cases). Other puncture wounds involved barbed wire, splinters, animal or insect bites, self-piercing, and self-performed tattoos. The environment in which acute injuries occurred was indoors or at home in 45%, in the yard, garden, or farm in 31%, and other outdoor locations in 23%.











Five percent of reported case-patients were intravenous drug users without other known injury, and 11% had chronic wounds. Twenty patients were reported to have received at least a primary series of tetanus toxoid; 18 had an outcome reported. Among these 18 patients, one (6%) death occurred; the death was in an injection-drug user whose last dose of tetanus toxoid was 11 years before the onset of tetanus. A total of 110 patients reported fewer than three doses of tetanus toxoid or had an unknown vaccination history; 95 of these patients had an outcome reported. Nineteen (20%) deaths occurred among these 95 patients.

Tetanus Toxoid

Characteristics

Tetanus toxoid was first produced in 1924, and tetanus toxoid immunizations were used extensively in the armed services during World War II. Tetanus cases among this population declined from 70 in World War I (13.4/100,000 wounds and injuries) to 12 in World War II (0.44/100,000). Of the 12 case-patients, half had received no prior toxoid.

DTaP, DT, Td and Tdap

	Diphtheria	Tetanus
DTaP, DT	7-8 Lf units	5-12.5 Lf units
Td, Tdap (adult)	2-2.5 Lf units	5 Lf units

DTaP and pediatric DT used through age 6 years. Adult Td for persons 7 years and older. Tdap for persons 10-18 years (Boostrix) or 10-64 years (Adacel)

Tetanus toxoid consists of a formaldehyde-treated toxin. The toxoid is standardized for potency in animal tests according to Food and Drug Administration (FDA) regulations. Occasionally, potency is mistakenly equated with Lf units, which are a measure of the quantity of toxoid, not its potency in inducing protection.

There are two types of toxoid available—adsorbed (aluminum salt precipitated) toxoid and fluid toxoid. Although the rates of seroconversion are about equal, the adsorbed toxoid is preferred because the antitoxin response reaches higher titers and is longer lasting than that following the fluid toxoid.

Tetanus Toxoid

- Formalin-inactivated tetanus toxin
- Schedule Three or four doses + booster
Booster every 10 years
- Efficacy Approximately 100%
- Duration Approximately 10 years
- Should be administered with diphtheria toxoid as DTaP, DT, Td, or Tdap

Tetanus toxoid is available as a single-antigen preparation, combined with diphtheria toxoid as pediatric diphtheria-tetanus toxoid (DT) or adult tetanus-diphtheria (Td), and with both diphtheria toxoid and acellular pertussis vaccine as DTaP or Tdap. Tetanus toxoid is also available as combined DTaP-HepB-IPV (Pediarix) and DTaP-IPV/Hib (Pentacel—see Chapter 14 for more information). Pediatric formulations (DT and DTaP) contain a similar amount of tetanus toxoid as adult Td, but contain 3 to 4 times as much diphtheria toxoid. Children younger than 7 years of age should receive either DTaP or pediatric DT. Persons 7 years of age or older should receive the adult formulation (adult Td), even if they have not completed a series of DTaP or pediatric DT. The use of single-antigen tetanus toxoid is not recommended. Tetanus toxoid should be given in combination with diphtheria toxoid, since periodic boosting is needed for both antigens. Two brands of Tdap are available: Boostrix (approved for

persons 10 through 64 years of age) and Adacel (approved for persons 11 through 64 years of age). DTaP and Tdap vaccines do not contain thimerosal as a preservative.

Immunogenicity and Vaccine Efficacy

After a primary series (three properly spaced doses of tetanus toxoid in persons 7 years of age and older, and four doses in children younger than 7 years of age) essentially all recipients achieve antitoxin levels considerably greater than the protective level of 0.1 IU/mL.

Efficacy of the toxoid has never been studied in a vaccine trial. It can be inferred from protective antitoxin levels that a complete tetanus toxoid series has a clinical efficacy of virtually 100%; cases of tetanus occurring in fully immunized persons whose last dose was within the last 10 years are extremely rare.

Antitoxin levels decrease with time. While some persons may be protected for life, by 10 years after the last dose, most persons have antitoxin levels that only approach the minimal protective level. As a result, routine boosters are recommended every 10 years.

In a small percentage of individuals, antitoxin levels fall below the minimal protective level before 10 years have elapsed. To ensure adequate protective antitoxin levels, persons who sustain a wound that is other than clean and minor should receive a tetanus booster if more than 5 years have elapsed since their last dose. (See Wound Management for details on persons who previously received fewer than three doses.)

Vaccination Schedule and Use

DTaP (diphtheria and tetanus toxoids and acellular pertussis vaccine) is the vaccine of choice for children 6 weeks through 6 years of age. The usual schedule is a primary series of four doses at 2, 4, 6, and 15–18 months of age. The first, second, and third doses of DTaP should be separated by a minimum of 4 weeks. The fourth dose should follow the third dose by no less than 6 months and should not be administered before 12 months of age.

If a child has a valid contraindication to pertussis vaccine, pediatric DT should be used to complete the vaccination series. If the child was younger than 12 months old when the first dose of DT was administered (as DTaP or DT), the child should receive a total of four primary DT doses. If the child was 12 months of age or older at the time that the first dose of DT was administered, three doses (third dose 6–12 months after the second) completes the primary DT series.

Routine DTaP Primary Vaccination Schedule

Dose	Age	Interval
Primary 1	2 months	---
Primary 2	4 months	4 weeks
Primary 3	6 months	4 weeks
Primary 4	15-18 months	6 months

Children Who Receive DT

- The number of doses of DT needed to complete the series depends on the child's age at the first dose:
  - –if first dose given at younger than 12 months of age, 4 doses are recommended
  - –if first dose given at 12 months or older, 3 doses complete the primary series

If the fourth dose of DTaP, DTP, or DT is administered before the fourth birthday, a booster dose is recommended at 4–6 years of age. The fifth dose is not required if the fourth dose was given on or after the fourth birthday.

Because of waning antitoxin titers, most persons have antitoxin levels below the optimal level 10 years after the last dose of DTaP, DTP, DT, or Td. Additional booster doses of tetanus and diphtheria toxoids are required every 10 years to maintain protective antitoxin titers. The first booster dose of Td may be given at 11 or 12 years of age if at least 5 years have elapsed since the last dose of DTaP, DTP, or DT. The Advisory Committee on Immunization Practices (ACIP) recommends that this dose be administered as Tdap. If a dose is given sooner as part of wound management, the next booster is not needed for 10 years thereafter. More frequent boosters are not indicated and have been reported to result in an increased incidence and severity of local adverse reactions.

Td is the vaccine of choice for children 7 years and older and for adults. A primary series is three or four doses, depending on whether the person has received prior doses of diphtheria-containing vaccine and the age these doses were administered. The number of doses recommended for children who received one or more doses of DTP, DTaP, or DT before age 7 years is discussed above. For unvaccinated persons 7 years and older (including persons who cannot document prior vaccination), the primary series is three doses. The first two doses should be separated by at least 4 weeks, and the third dose given 6 to 12 months after the second. ACIP recommends that *one* of these doses (preferably the first) be administered as Tdap. A booster dose of Td should be given every 10 years. Tdap is approved for a single dose at this time (i.e., it should not be used for all the doses of Td in a previously unvaccinated person 7 years or older). Refer to the pertussis chapter for more information about Tdap.

Interruption of the recommended schedule or delay of subsequent doses does not reduce the response to the vaccine when the series is finally completed. There is no need to restart a series regardless of the time elapsed between doses.

Tetanus disease does not confer immunity because of the very small amount of toxin required to produce illness. Persons recovering from tetanus should begin or complete active immunization with tetanus toxoid (Td) during convalescence.

Routine DTaP Schedule
Children Younger Than 7 years of Age

Booster Doses

- 4 through 6 years of age, before entering school
- 11 or 12 years of age if 5 years since last dose (Tdap)
- Every 10 years thereafter (Td)

Routine Td Schedule
Unvaccinated Persons 7 Years of Age or Older

Dose*	Interval
Primary 1	---
Primary 2	4 weeks
Primary 3	6 to 12 months

Booster dose every 10 years

*ACIP recommends that one of these doses (preferably the first) be administered as Tdap

Diphtheria and Tetanus Toxoids
Contraindications and Precautions

- Severe allergic reaction to vaccine component or following a prior dose
- Moderate or severe acute illness

Contraindications and Precautions to Vaccination

A severe allergic reaction (anaphylaxis) to a vaccine component or following a prior dose of tetanus toxoid is a contraindication to receipt of tetanus toxoid. If a generalized reaction is suspected to represent allergy, it may be

useful to refer an individual for appropriate skin testing before discontinuing tetanus toxoid immunization. A moderate or severe acute illness is reason to defer routine vaccination, but a minor illness is not.

If a contraindication to using tetanus toxoid-containing preparations exists, passive immunization with tetanus immune globulin (TIG) should be considered whenever an injury other than a clean minor wound is sustained.

See Chapter 14, Pertussis, for additional information on contraindications and precautions to Tdap.

Adverse Reactions Following Vaccination

Local adverse reactions (e.g., erythema, induration, pain at the injection site) are common but are usually self-limited and require no therapy. A nodule may be palpable at the injection site of adsorbed products for several weeks. Abscess at the site of injection has been reported. Fever and other systemic symptoms are not common.

Diphtheria and Tetanus Toxoids Adverse Reactions

- Local reactions (erythema, induration)
- Fever and systemic symptoms not common
- Exaggerated local reactions (Arthus-type)
- Severe systemic reactions rare

Exaggerated local (Arthus-like) reactions are occasionally reported following receipt of a diphtheria- or tetanus-containing vaccine. These reactions present as extensive painful swelling, often from shoulder to elbow. They generally begin from 2 to 8 hours after injections and are reported most often in adults, particularly those who have received frequent doses of diphtheria or tetanus toxoid. Persons experiencing these severe reactions usually have very high serum antitoxin levels; they should not be given further routine or emergency booster doses of Td more frequently than every 10 years. Less severe local reactions may occur in persons who have multiple prior boosters.

Severe systemic reactions such as generalized urticaria (hives), anaphylaxis, or neurologic complications have been reported after receipt of tetanus toxoid. A few cases of peripheral neuropathy and Guillain-Barré syndrome (GBS) have been reported following tetanus toxoid administration. The Institute of Medicine has concluded that the available evidence favors a causal relationship between tetanus toxoid and both brachial neuritis and GBS, although these reactions are very rare.

Vaccine Storage and Handling

All tetanus-toxoid-containing vaccines should be stored at 35°–46°F (2°–8°C). Freezing reduces the potency of the tetanus component. Vaccine exposed to freezing temperature should never be administered.

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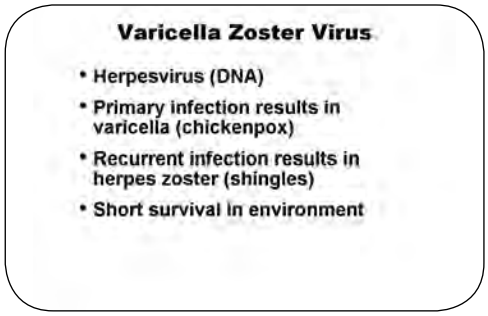
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Varicella

Varicella is an acute infectious disease caused by varicella zoster virus (VZV). The recurrent infection (herpes zoster, also known as shingles) has been recognized since ancient times. Primary varicella infection (chickenpox) was not reliably distinguished from smallpox until the end of the 19th century. In 1875, Steiner demonstrated that chickenpox was caused by an infectious agent by inoculating volunteers with the vesicular fluid from a patient with acute varicella. Clinical observations of the relationship between varicella and herpes zoster were made in 1888 by von Bokay, when children without evidence of varicella immunity acquired varicella after contact with herpes zoster. VZV was isolated from vesicular fluid of both chickenpox and zoster lesions in cell culture by Thomas Weller in 1954. Subsequent laboratory studies of the virus led to the development of a live attenuated varicella vaccine in Japan in the 1970s. The vaccine was licensed for use in the United States in March 1995. The first vaccine to reduce the risk of herpes zoster was licensed in May 2006.

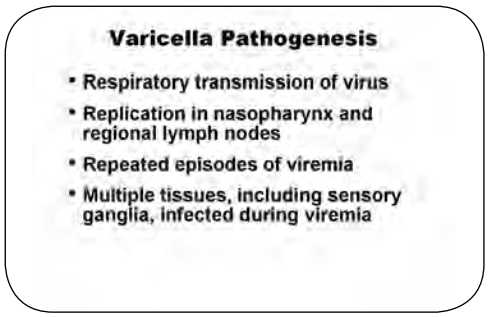
Varicella Zoster Virus

VZV is a DNA virus and is a member of the herpesvirus group. Like other herpesviruses, VZV has the capacity to persist in the body after the primary (first) infection as a latent infection. VZV persists in sensory nerve ganglia. Primary infection with VZV results in chickenpox. Herpes zoster (shingles) is the result of recurrent infection. The virus is believed to have a short survival time in the environment.



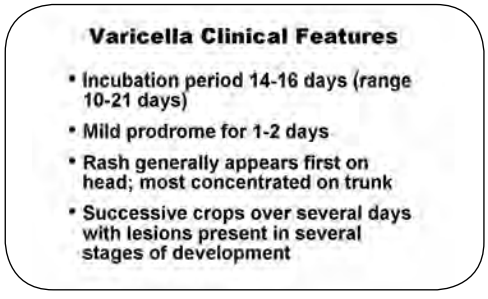
Pathogenesis

VZV enters through the respiratory tract and conjunctiva. The virus is believed to replicate at the site of entry in the nasopharynx and in regional lymph nodes. A primary viremia occurs 4 to 6 days after infection and disseminates the virus to other organs, such as the liver, spleen, and sensory ganglia. Further replication occurs in the viscera, followed by a secondary viremia, with viral infection of the skin. Virus can be cultured from mononuclear cells of an infected person from 5 days before to 1 or 2 days after the appearance of the rash.



Clinical Features

The incubation period is 14 to 16 days after exposure, with a range of 10 to 21 days. The incubation period may be prolonged in immunocompromised patients and those who have received postexposure treatment with a varicella antibody–containing product.



Varicella

Primary Infection (Chickenpox)

A mild prodrome may precede the onset of a rash. Adults may have 1 to 2 days of fever and malaise prior to rash onset, but in children the rash is often the first sign of disease.

The rash is generalized and pruritic and progresses rapidly from macules to papules to vesicular lesions before crusting. The rash usually appears first on the head, then on the trunk, and then the extremities; the highest concentration of lesions is on the trunk (centripetal distribution). Lesions also can occur on mucous membranes of the oropharynx, respiratory tract, vagina, conjunctiva, and the cornea. Lesions are usually 1 to 4 mm in diameter. The vesicles are superficial and delicate and contain clear fluid on an erythematous base. Vesicles may rupture or become purulent before they dry and crust. Successive crops appear over several days, with lesions present in several stages of development. For example, macular lesions may be observed in the same area of skin as mature vesicles. Healthy children usually have 200 to 500 lesions in 2 to 4 successive crops.

The clinical course in healthy children is generally mild, with malaise, pruritus (itching), and temperature up to 102°F for 2 to 3 days. Adults may have more severe disease and have a higher incidence of complications. Respiratory and gastrointestinal symptoms are absent. Children with lymphoma and leukemia may develop a severe progressive form of varicella characterized by high fever, extensive vesicular eruption, and high complication rates. Children infected with human immunodeficiency virus also may have severe, prolonged illness.

Recovery from primary varicella infection usually results in lifetime immunity. In otherwise healthy persons, a second occurrence of chickenpox is not common, but it can happen, particularly in immunocompromised persons. As with other viral diseases, reexposure to natural (wild) varicella may lead to reinfection that boosts antibody titers without causing clinical illness or detectable viremia.

Recurrent Disease (Herpes Zoster)

Herpes Zoster (Shingles)

- Reactivation of varicella zoster virus
- Associated with:
  - aging
  - immunosuppression
  - intrauterine exposure
  - varicella at younger than 18 months of age

Herpes zoster, or shingles, occurs when latent VZV reactivates and causes recurrent disease. The immunologic mechanism that controls latency of VZV is not well understood. However, factors associated with recurrent disease include aging, immunosuppression, intrauterine exposure to VZV, and having had varicella at a young age (younger than 18 months). In immunocompromised persons, zoster may disseminate, causing generalized skin lesions and central nervous system, pulmonary, and hepatic involvement.

The vesicular eruption of zoster generally occurs unilaterally in the distribution of a sensory nerve. Most often,

this involves the trunk or the fifth cranial nerve. Two to four days prior to the eruption, there may be pain and paresthesia in the involved area. There are few systemic symptoms.

Complications

Varicella

Acute varicella is generally mild and self-limited, but it may be associated with complications. Secondary bacterial infections of skin lesions with *Staphylococcus* or *Streptococcus* are the most common cause of hospitalization and outpatient medical visits. Secondary infection with invasive group A streptococci may cause serious illness and lead to hospitalization or death. Pneumonia following varicella is usually viral but may be bacterial. Secondary bacterial pneumonia is more common in children younger than 1 year of age. Central nervous system manifestations of varicella range from aseptic meningitis to encephalitis. Involvement of the cerebellum, with resulting cerebellar ataxia, is the most common and generally has a good outcome. Encephalitis is an infrequent complication of varicella (estimated 1.8 per 10,000 cases) and may lead to seizures and coma. Diffuse cerebral involvement is more common in adults than in children. Reye syndrome is an unusual complication of varicella and influenza and occurs almost exclusively in children who take aspirin during the acute illness. The etiology of Reye syndrome is unknown. There has been a dramatic decrease in the incidence of Reye syndrome during the past decade, presumably related to decreased use of aspirin by children.

Varicella Complications

- Bacterial infection of skin lesions
- Pneumonia (viral or bacterial)
- Central nervous system manifestations
- Reye syndrome
- Hospitalization: 2-3 per 1,000 cases
- Death: 1 per 60,000 cases
- Postherpetic neuraligia (complication of zoster)

Rare complications of varicella include aseptic meningitis, transverse myelitis, Guillain-Barré syndrome, thrombocytopenia, hemorrhagic varicella, purpura fulminans, glomerulonephritis, myocarditis, arthritis, orchitis, uveitis, iritis, and hepatitis.

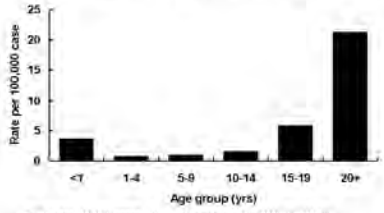
In the prevaccine era, approximately 11,000 persons with varicella required hospitalization each year. Hospitalization rates were approximately 2–3 per 1,000 cases among healthy children and 8 per 1,000 cases among adults. Death occurred in approximately 1 in 60,000 cases. From 1990 through 1996, an average of 103 deaths from varicella were reported each year. Most deaths occur in immunocompetent children and adults. Since 1996, the number of hospitalizations and deaths from varicella has declined more than 90%.

Groups at Increased Risk of Complications of Varicella

- Persons older than 15 years
- Infants younger than 1 year
- Immunocompromised persons
- Newborns of women with rash onset within 5 days before to 2 days after delivery

The risk of complications from varicella varies with age. Complications are infrequent among healthy children. They occur much more frequently in persons older than 15 years of age and infants younger than 1 year of age. For instance, among children 1–14 years of age, the fatality rate of vari-

Varicella Fatality Rate-United States, 1990-1994



*Deaths per 100,000 cases. Meyer et al. J Infect Dis 2000;182:383-90

cella is approximately 1 per 100,000 cases, among persons 15–19 years, it is 2.7 per 100,000 cases, and among adults 30–49 years of age, 25.2 per 100,000 cases. Adults account for only 5% of reported cases of varicella but approximately 35% of mortality.

Immunocompromised persons have a high risk of disseminated disease (up to 36% in one report). These persons may have multiple organ system involvement, and the disease may become fulminant and hemorrhagic. The most frequent complications in immunocompromised persons are pneumonia and encephalitis. Children with HIV infection are at increased risk for morbidity from varicella and herpes zoster.

The onset of maternal varicella from 5 days before to 2 days after delivery may result in overwhelming infection of the neonate and a fatality rate as high as 30%. This severe disease is believed to result from fetal exposure to varicella virus without the benefit of passive maternal antibody. Infants born to mothers with onset of maternal varicella 5 days or more prior to delivery usually have a benign course, presumably due to passive transfer of maternal antibody across the placenta.

Herpes Zoster

Postherpetic neuralgia, or pain in the area of the ocurrence that persists after the lesions have resolved, is a distressing complication of zoster. There is currently no adequate therapy available. Postherpetic neuralgia may last a year or longer after the episode of zoster. Ocular nerve and other organ involvement with zoster can occur, often with severe sequelae.

Congenital VZV Infection

Primary maternal varicella infection in the first 20 weeks of gestation is occasionally associated with a variety of abnormalities in the newborn, including low birth weight, hypoplasia of an extremity, skin scarring, localized muscular atrophy, encephalitis, cortical atrophy, chorioretinitis, and microcephaly. This constellation of abnormalities, collectively known as congenital varicella syndrome, was first recognized in 1947. The risk of congenital abnormalities from primary maternal varicella infection appears to be very low (less than 2%). Rare reports of congenital birth defects following maternal zoster exist, but virologic confirmation of maternal lesions is lacking.

Congenital Varicella Syndrome

- Results from maternal infection during pregnancy
- Low birth weight, atrophy of extremity with skin scarring, eye and neurologic abnormalities
- Risk appears to be low (less than 2%)
- Period of risk may extend through first 20 weeks of pregnancy

Laboratory Diagnosis

Laboratory diagnosis is not routinely required, but is useful if confirmation of the diagnosis or determination of susceptibility is necessary. Varicella incidence has declined

dramatically as a result of routine varicella immunization in the United States. This has had the combined effect of increasing the number of atypical cases (either vaccine adverse events or breakthrough wild-type infection in immunized persons) and of reducing physicians' experience in diagnosing varicella. As a result, the need for laboratory confirmation of varicella has increased.

Varicella Laboratory Diagnosis

- Isolation of varicella virus from clinical specimen
- Rapid varicella virus identification using PCR (preferred, if available) or DFA
- Significant rise in varicella IgG by any standard serologic assay (e.g., enzyme immunoassay)

Varicella zoster virus may be isolated in tissue culture. The most frequent source of isolation is vesicular fluid. Laboratory techniques allow differentiation of wild-type and vaccine strains of VZV.

Rapid varicella virus identification techniques are indicated for a case with severe or unusual disease to initiate specific antiviral therapy. VZV polymerase chain reaction (PCR) is the method of choice for rapid clinical diagnosis. Real-time PCR methods are widely available and are the most sensitive and specific method of the available tests. Results are available within several hours. If real-time PCR is unavailable, the direct fluorescent antibody (DFA) method can be used, although it is less sensitive than PCR and requires more meticulous specimen collection and handling.

Specimens are best collected by unroofing a vesicle, preferably a fresh fluid-filled vesicle, and then rubbing the base of a skin lesion with a polyester swab. Crusts from lesions are also excellent specimens for PCR. Other specimen sources such as nasopharyngeal secretions, saliva, blood, urine, bronchial washings, and cerebrospinal fluid are considered less desirable sources than skin lesions because positive test results from such specimens are much less likely. Because viral proteins persist after cessation of viral replication, PCR and DFA may be positive when viral cultures are negative. Additional information concerning virus isolation and strain differentiation can be found at http://www.cdc.gov/vaccines/pubs/surv-manual/downloads/chpt17_varicella.pdf

A reliable history of chickenpox has been found to be a valid measure of immunity to varicella because the rash is distinctive and subclinical cases are unusual. As a result, serologic testing of children is generally not necessary. However, serologic testing may be useful in adult vaccination programs. A variety of serologic tests for varicella antibody are available. Available tests include complement fixation (CF), indirect fluorescent antibody (IFA), fluorescent antibody to membrane antigen (FAMA), neutralization, indirect hemagglutination (IHA), immune adherence hemagglutination (IAHA), radioimmunoassay (RIA), latex agglutination (LA), and enzyme-linked immunosorbent assay (ELISA). ELISA is sensitive and specific, simple to perform, and widely available commercially. A commercially available LA is sensitive, simple, and rapid to perform. LA is generally more sensitive than commercial ELISAs, although it can

result in false-positive results, leading to failure to identify persons without evidence of varicella immunity. This latter concern can be minimized by performing LA as a dilution series. Either of these tests would be useful for screening for varicella immunity.

Antibody resulting from vaccination is generally of lower titer than antibody resulting from varicella disease. Commercial antibody assays, particularly the LA test, may not be sensitive enough to detect vaccine-induced antibody in some recipients. Because of the potential for false-negative serologic tests, routine postvaccination serologic testing is not recommended. For diagnosis of acute varicella infection, serologic confirmation would include a significant rise in varicella IgG by any standard serologic assay. Testing using commercial kits for IgM antibody is not recommended since available methods lack sensitivity and specificity; false-positive IgM results are common in the presence of high IgG levels. The National VZV Laboratory at CDC has developed a reliable IgM capture assay. Call 404-639-0066, 404-639-3667, or e-mail vzvlab@cdc.gov for details about collecting and submitting specimens for testing.

Epidemiology

Occurrence

Varicella and herpes zoster occur worldwide. Some data suggest that in tropical areas, varicella infection occurs more commonly among adults than children. The reason(s) for this difference in age distribution are not known with certainty, but may be related to lack of childhood varicella infection in rural populations.

Varicella Epidemiology

• Reservoir	Human
• Transmission	Airborne droplet Direct contact with lesions
• Temporal pattern	Peak in winter and early spring (U.S.)
• Communicability	1-2 days before to 4-5 days after onset of rash May be longer in immunocompromised

Reservoir

Varicella is a human disease. No animal or insect source or vector is known to exist.

Transmission

Infection with VZV occurs through the respiratory tract. The most common mode of transmission of VZV is believed to be person to person from infected respiratory tract secretions. Transmission may also occur by respiratory contact with airborne droplets or by direct contact or inhalation of aerosols from vesicular fluid of skin lesions of acute varicella or zoster.

Temporal Pattern

In temperate areas, varicella has a distinct seasonal fluctuation, with the highest incidence occurring in winter and early spring. In the United States, incidence is highest

between March and May and lowest between September and November. Less seasonality is reported in tropical areas. Herpes zoster has no seasonal variation and occurs throughout the year.

Communicability

The period of communicability extends from 1 to 2 days before the onset of rash through the first 4 to 5 days, or until lesions have formed crusts. Immunocompromised patients with varicella are probably contagious during the entire period new lesions are appearing. The virus has not been isolated from crusted lesions.

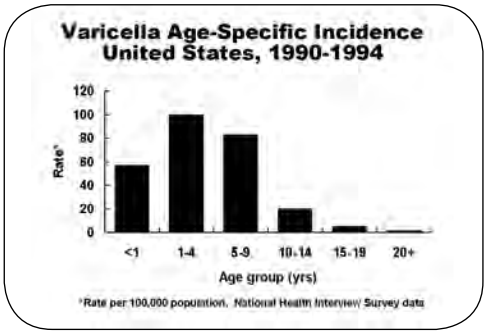
Varicella is highly contagious. It is less contagious than measles, but more so than mumps and rubella. Secondary attack rates among susceptible household contacts of persons with varicella are as high as 90% (that is, 9 of 10 susceptible household contacts of persons with varicella will become infected).

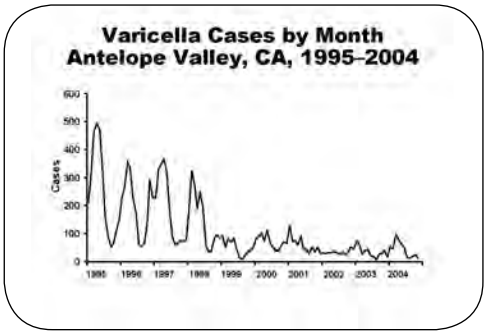
Secular Trends in the United States

Varicella

In the prevaccine era, varicella was endemic in the United States, and virtually all persons acquired varicella by adulthood. As a result, the number of cases occurring annually was estimated to approximate the birth cohort, or approximately 4 million per year. Varicella was removed from the list of nationally notifiable conditions in 1981, but some states continued to report cases to CDC. The majority of cases (approximately 85%) occurred among children younger than 15 years of age. The highest age-specific incidence of varicella was among children 1–4 years of age, who accounted for 39% of all cases. This age distribution was probably a result of earlier exposure to VZV in preschool and child care settings. Children 5–9 years of age accounted for 38% of cases. Adults 20 years of age and older accounted for only 7% of cases (National Health Interview Survey data, 1990–1994).

Data from three active varicella surveillance areas indicate that the incidence of varicella, as well as varicella-related hospitalizations, has decreased significantly since licensure of vaccine in 1995. In 2004, varicella vaccination coverage among children 19–35 months in two of the active surveillance areas was estimated to be 89% and 90%. Compared with 1995, varicella cases declined 83%–93% by 2004. Cases declined most among children aged 1–4 and 5–9 years, but a decline occurred in all age groups including infants and adults, indicating reduced transmission of the virus in these groups. The reduction of varicella cases is the result of the increasing use of varicella vaccine. Varicella vaccine

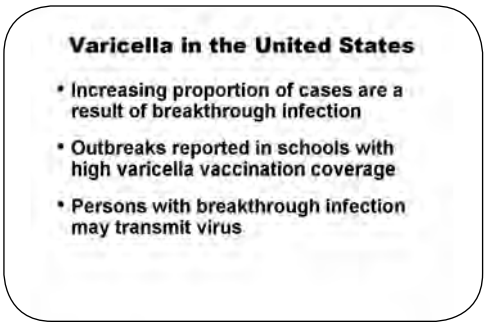




Reduction in Age-Specific Varicella Incidence Rate
Varicella Active Surveillance Project Sites, 1995 to 2004

Age group	Antelope Valley, CA* (%)	West Philadelphia (%)
< 1	83	77
1-4	94	89
5-9	83	95
10-14	49	98
15-19	65	78
20+	81	67
Total	83	93

*2003 population used for rate calculations

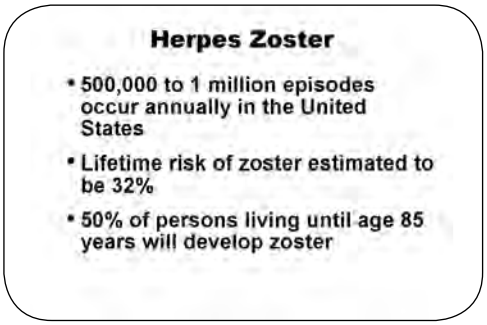


coverage among 19–35-month-old children was estimated by the National Immunization Survey to be 90% in 2007.

Despite high one-dose vaccination coverage and success of the vaccination program in reducing varicella morbidity and mortality, varicella surveillance indicates that the number of reported varicella cases appears to have plateaued. An increasing proportion of cases represent breakthrough infection (chickenpox occurring in a previously vaccinated person). In 2001–2005, outbreaks were reported in schools with high varicella vaccination coverage (96%–100%). These outbreaks had many similarities: all occurred in elementary schools; vaccine effectiveness was within the expected range (72%–85%); the highest attack rates occurred among the younger students; each outbreak lasted about 2 months; and persons with breakthrough infection transmitted the virus although the breakthrough disease was mild. Overall attack rates among vaccinated children were 11%–17%, with attack rates in some classrooms as high as 40%. These data indicate that even in settings where almost everyone was vaccinated and vaccine performed as expected, varicella outbreaks could not be prevented with the current one-dose vaccination policy. These observations led to the recommendation in 2006 for a second routine dose of varicella vaccine.

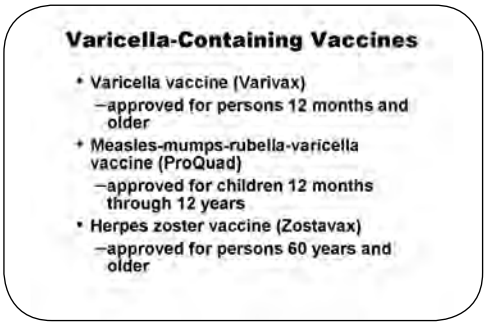
Herpes Zoster

Herpes zoster is not a notifiable condition. An estimated 500,000 to 1 million episodes of zoster occur annually in the United States. The lifetime risk of zoster is estimated to be at least 32%. Increasing age and cellular immunosuppression are the most important risk factors; 50% of persons living until age 85 years will develop zoster.



Vaccines Containing Varicella Virus

Three varicella-containing vaccines are now approved for use in the United States: varicella vaccine (Varivax), combination measles-mumps-rubella-varicella (MMRV) vaccine (ProQuad), and herpes zoster vaccine (Zostavax).



Characteristics

Varicella Vaccine

Varicella vaccine (Varivax, Merck) is a live attenuated viral vaccine, derived from the Oka strain of VZV. The vaccine virus was isolated by Takahashi in the early 1970s from vesicular fluid from an otherwise healthy child with varicella disease. Varicella vaccine was licensed for general use in Japan and Korea in 1988. It was licensed in the United States in 1995 for persons 12 months of age and older. The virus was attenuated by sequential passage in human embryonic lung cell culture, embryonic guinea pig fibroblasts, and

in WI-38 human diploid cells. The Oka/Merck vaccine has undergone further passage through MRC-5 human diploid cell cultures for a total of 31 passages. The reconstituted vaccine contains small amounts of sucrose, processed porcine gelatin, sodium chloride, monosodium L-glutamate, sodium diphosphate, potassium phosphate, and potassium chloride, and trace quantities of residual components of MRC-5 cells (DNA and protein), EDTA, neomycin, and fetal bovine serum. The vaccine is reconstituted with sterile water and contains no preservative.

Measles-Mumps-Rubella-Varicella Vaccine

In September 2005, the Food and Drug Administration (FDA) licensed a combined live attenuated measles-mumps-rubella and varicella vaccine (ProQuad, Merck) for use in persons 12 months through 12 years of age. The attenuated measles, mumps, and rubella vaccine viruses in MMRV are identical and of equal titer to those in the measles-mumps-rubella (MMR) vaccine. The titer of Oka/Merck varicella zoster virus is higher in MMRV vaccine than in single-antigen varicella vaccine, a minimum of 9,772 (3.99 $\log^{10}$) plaque-forming units (PFU) versus 1,350 PFU (~3.13 $\log^{10}$), respectively. Each 0.5-mL dose contains a small quantity of sucrose, hydrolyzed gelatin, sodium chloride, sorbitol, monosodium L-glutamate, sodium phosphate dibasic, human albumin, sodium bicarbonate, potassium phosphate monobasic, potassium chloride; potassium phosphate dibasic; residual components of MRC-5 cells (DNA and protein) neomycin, bovine calf serum, and other buffer and media ingredients. The vaccine is reconstituted with sterile water and contains no preservative.

Herpes Zoster Vaccine

In May 2006, the FDA approved herpes zoster vaccine (Zostavax, Merck) for use in persons 60 years of age and older. The vaccine contains the same Oka/Merck varicella zoster virus used in varicella and MMRV vaccines but at a much higher titer (a minimum of 19,400 PFU versus 1,350 PFU in varicella vaccine). Each 0.65-mL dose contains a small amount of sucrose, hydrolyzed porcine gelatin, sodium chloride, monosodium L-glutamate, sodium phosphate dibasic, potassium phosphate monobasic, potassium chloride; residual components of MRC-5 cells including (DNA and protein); neomycin and bovine calf serum. The vaccine is reconstituted with sterile water and contains no preservative.

Immunogenicity and Vaccine Efficacy

Varicella Vaccine

After one dose of single-antigen varicella vaccine, 97% of children 12 months to 12 years of age develop detectable antibody titers. More than 90% of vaccine responders

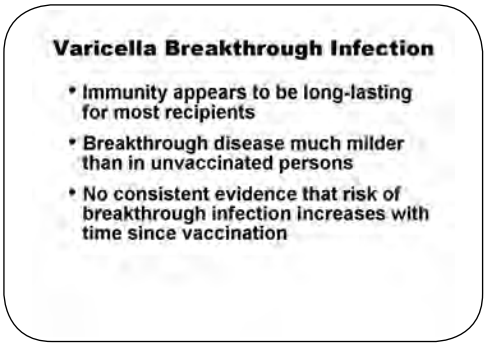
Varicella Vaccine Immunogenicity and Efficacy

- Detectable antibody
  - –97% of children 12 months-12 years following 1 dose
  - –99% of persons 13 years and older after 2 doses
- 70%-90% effective against any varicella disease
- 95%-100% effective against severe varicella disease

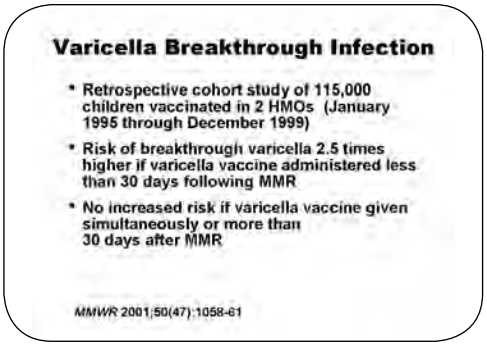
maintain antibody for at least 6 years. In Japanese studies, 97% of children had antibody 7 to 10 years after vaccination. Vaccine efficacy is estimated to be 70% to 90% against infection, and 90% to 100% against moderate or severe disease.

Among healthy adolescents and adults 13 years of age and older, an average of 78% develop antibody after one dose, and 99% develop antibody after a second dose given 4 to 8 weeks later. Antibody persisted for at least 1 year in 97% of vaccinees after the second dose given 4 to 8 weeks after the first dose.

Immunity appears to be long-lasting, and is probably permanent in the majority of vaccinees. Breakthrough infection is significantly milder, with fewer lesions (generally fewer than 50), many of which are maculopapular rather than vesicular. Most persons with breakthrough infection do not have fever.



Although findings of some studies have suggested otherwise, most investigations have not identified time since vaccination as a risk factor for breakthrough varicella. Some, but not all, recent investigations have identified the presence of asthma, use of steroids, and vaccination at younger than 15 months of age as risk factors for breakthrough varicella. Breakthrough varicella infection could be a result of several factors, including interference of vaccine virus replication by circulating antibody, impotent vaccine resulting from storage or handling errors, or inaccurate recordkeeping.



Interference from live viral vaccine administered before varicella vaccine could also reduce vaccine effectiveness. A study of 115,000 children in two health maintenance organizations during 1995–1999 found that children who received varicella vaccine less than 30 days after MMR vaccination had a 2.5-fold increased risk of breakthrough varicella compared with those who received varicella vaccine before, simultaneously with, or more than 30 days after MMR.

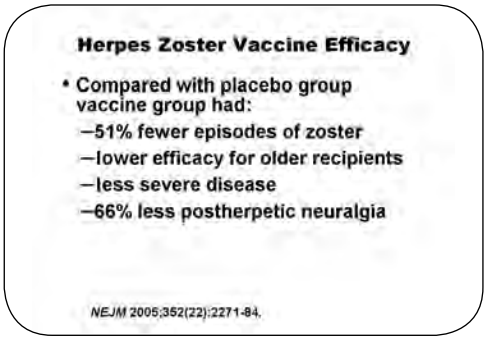
Studies have shown that a second dose of varicella vaccine boosts immunity and reduces breakthrough disease in children.

MMRV Vaccine

MMRV vaccine was licensed on the basis of equivalence of immunogenicity of the antigenic components rather than the clinical efficacy. Clinical studies involving healthy children age 12–23 months indicated that those who received a single dose of MMRV vaccine developed similar levels of antibody to measles, mumps, rubella and varicella as children who received MMR and varicella vaccines concomitantly at separate injection sites.

Herpes Zoster Vaccine

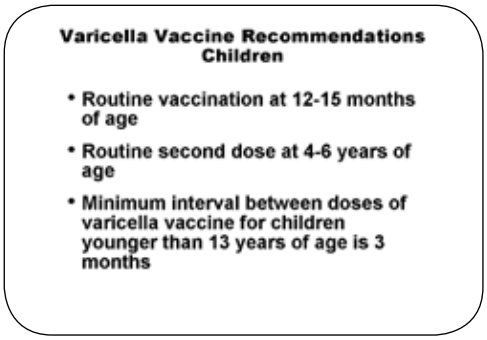
The primary clinical trial for zoster vaccine included more than 38,000 adults 60 to 80 years of age with no history of prior shingles. Participants were followed for a median of 3.1 years after a single dose of vaccine. Compared with the placebo group, the vaccine group had 51% fewer episodes of zoster. Efficacy was highest for persons 60–69 years of age (64%) and declined with increasing age. Efficacy was 18% for participants 80 years or older. Vaccine recipients who developed zoster generally had less severe disease. Vaccine recipients also had about 66% less postherpetic neuralgia, the pain that can persist long after the shingles rash has resolved. The duration of reduction of risk of zoster is not known.



Vaccination Schedule and Use

Varicella Vaccine

Varicella virus vaccine is recommended for all children without contraindications at 12 through15 months of age. The vaccine may be given to all children at this age regardless of prior history of varicella.



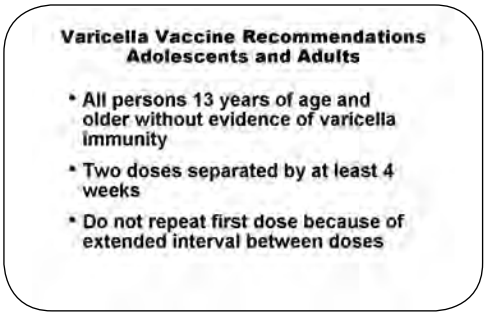
A second dose of varicella vaccine should be administered at 4 through 6 years of age, at the same visit as the second dose of MMR vaccine. The second dose may be administered earlier than 4 through 6 years of age if at least 3 months have elapsed following the first dose (i.e., the minimum interval between doses of varicella vaccine for children younger than 13 years is 3 months). However, if the second dose is administered at least 28 days following the first dose, the second dose does not need to be repeated. A second dose of varicella vaccine is also recommended for persons older than 4 through 6 years of age who have received only one dose. Varicella vaccine doses administered to persons 13 years or older should be separated by 4 to 8 weeks.

All varicella-containing vaccines should be administered by the subcutaneous route. Varicella vaccine has been shown to be safe and effective in healthy children when administered at the same time as MMR vaccine at separate sites and with separate syringes. If varicella and MMR vaccines are not administered at the same visit, they should be separated by at least 28 days. Varicella vaccine may also be administered simultaneously (but at separate sites with separate syringes) with all other childhood vaccines. ACIP strongly recommends that varicella vaccine be administered simultaneously with all other vaccines recommended at 12 through 15 months of age.

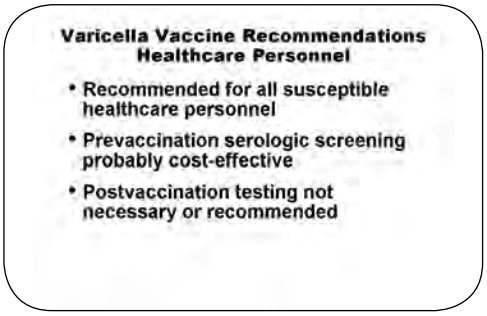
Children with a clinician-diagnosed or verified history of typical chickenpox can be assumed to be immune to varicella. Serologic testing of such children prior to vaccination

is not warranted because the majority of children between 12 months and 12 years of age without a clinical history of chickenpox are not immune. Prior history of chickenpox is not a contraindication to varicella vaccination.

Varicella vaccine should be administered to all adolescents and adults 13 years of age and older who do not have evidence of varicella immunity (see Varicella Immunity section). Persons 13 years of age and older should receive two doses of varicella vaccine separated by at least 4 weeks. If there is a lapse of more than 4 weeks after the first dose, the second dose may be administered at any time without repeating the first dose.



Assessment of varicella immunity status of all adolescents and adults and vaccination of those who lack evidence of varicella immunity are desirable to protect these individuals from the higher risk of complications from acquired varicella. Vaccination may be offered at the time of routine healthcare visits. However, specific assessment efforts should be focused on adolescents and adults who are at highest risk of exposure and those most likely to transmit varicella to others.



The ACIP recommends that all healthcare personnel be immune to varicella. In healthcare settings, serologic screening of personnel who are uncertain of their varicella history, or who claim not to have had the disease is likely to be cost-effective. Testing for varicella immunity following two doses of vaccine is not necessary because 99% of persons are seropositive after the second dose. Moreover, available commercial assays are not sensitive enough to detect antibody following vaccination in all instances.

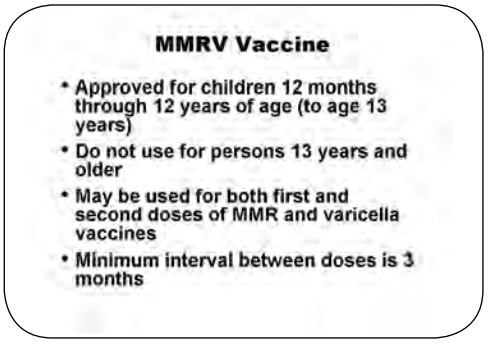
Seroconversion does not always result in full protection against disease, although no data regarding correlates of protection are available for adults. If a vaccinated healthcare provider is exposed to VZV, the employee should be monitored daily from day 10 to day 21 after exposure through the employee health or infection control program to determine clinical status (screen for fever, skin lesions, and systemic symptoms). Persons with varicella may be infectious starting 2 days before rash onset. In addition, the healthcare providershould be instructed to immediately report fever, headache, or other constitutional symptoms and any skin lesions (which may be atypical). The person should be placed on sick leave immediately if symptoms occur.

The risk of transmission of vaccine virus from a vaccinated person to a susceptible contact appears to be very low (see Transmission of Varicella Vaccine Virus section), and the benefits of vaccinating susceptible healthcare providers clearly outweigh this potential risk. Transmission of vaccine virus appears to occur primarily if and when the vaccinee develops a vaccine-associated rash. As a safeguard, medical

facilities may wish to consider protocols for personnel who develop a rash following vaccination (e.g., avoidance of contact with persons at high risk of serious complications, such as immunosuppressed persons who do not have evidence of varicella immunity).

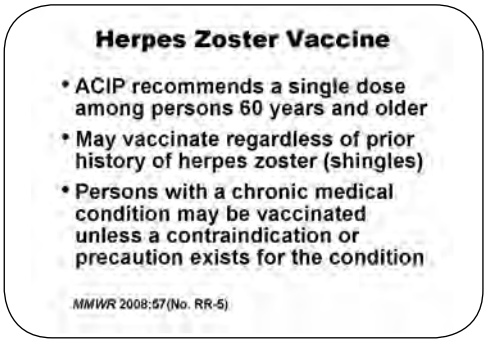
MMRV Vaccine

MMRV vaccine is indicated for vaccination against measles, mumps, rubella and varicella in children 12 months through 12 years of age. Persons 13 years of age and older should not receive MMRV. When used, MMRV vaccine should be administered on or after the first birthday, preferably as soon as the child becomes eligible for vaccination. MMRV may be used for both the first and second doses of MMR and varicella in children younger than 13 years. The minimum interval between doses of MMRV is 3 months. However, if the second dose is administered at least 28 days following the first dose, the second dose does not need to be repeated.



Herpes Zoster Vaccine

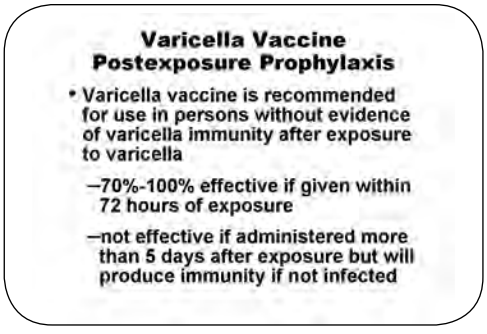
Zoster vaccine is approved by FDA for persons 60 years and older. ACIP recommends a single dose of zoster vaccine for adults 60 years of age and older whether or not they report a prior episode of herpes zoster. Persons with a chronic medical condition may be vaccinated unless a contraindication or precaution exists for the condition (see Conraindications and Precautions to Vaccination).



Postexposure Prophylaxis

Varicella Vaccine

Data from the United States and Japan in a variety of settings indicate that varicella vaccine is 70% to 100% effective in preventing illness or modifying the severity of illness if used within 3 days, and possibly up to 5 days, after exposure. ACIP recommends the vaccine for use in persons who do not have evidence of varicella immunity following exposure to varicella. If exposure to varicella does not cause infection, postexposure vaccination should induce protection against subsequent exposure. If the exposure results in infection, there is no evidence that administration of varicella vaccine during the incubation period or prodromal stage of illness increases the risk for vaccine-associated adverse reactions. Although postexposure use of varicella vaccine has potential applications in hospital settings, preexposure vaccination of all healthcare workers without evidence of varicella immunity is the recommended and preferred method for preventing varicella in healthcare settings.



Varicella outbreaks in some settings (e.g., child care facilities and schools) can persist up to 6 months. Varicella vaccine has been used successfully to control these outbreaks. The ACIP recommends a second dose of varicella vaccine for outbreak control. During a varicella outbreak, persons who have received one dose of varicella vaccine should receive a second dose, provided the appropriate vaccination interval has elapsed since the first dose (3 months for persons aged 12 months to 12 years and at least 4 weeks for persons aged 13 years of age and older).

MMRV Vaccine

MMRV vaccine may be used as described for varicella vaccine, and for measles as described in Chapter 11, Measles.

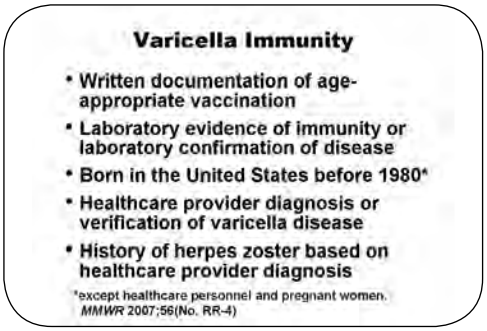
Herpes Zoster Vaccine

Exposure to a person with either primary varicella (chickenpox) or herpes zoster does not cause zoster in the exposed person. Herpes zoster vaccine has no role in the postexposure management of either chickenpox or zoster and should not be used for this purpose.

Varicella Immunity

In 2007, the ACIP published a revised definition for evidence of immunity to varicella. Evidence of immunity to varicella includes any of the following:

- Documentation of age-appropriate vaccination:
  - Preschool-aged children 12 months of age or older: one dose
  - School-aged children, adolescents, and adults: two doses
- Laboratory evidence of immunity or laboratory confirmation of disease. Commercial assays can be used to assess disease -induced immunity, but they lack adequate sensitivity to reliably detect vaccine-induced immunity (i.e., they may yield false-negative results).
- Born in the United States before 1980. For healthcare providers and pregnant women, birth before 1980 should not be considered evidence of immunity. Persons born outside the United States should meet one of the other criteria for varicella immunity.
- A healthcare provider diagnosis or verification of varicella disease. Verification of history or diagnosis of typical disease can be done by any healthcare provider (e.g., school or occupational clinic nurse, nurse practitioner, physician assistant, physician). For persons reporting a history of or presenting with atypical and/or mild



cases, assessment by a physician or designee is recommended, and one of the following should be sought: a) an epidemiologic link to a typical varicella case, or b) evidence of laboratory confirmation if laboratory testing was performed at the time of acute disease. When such documentation is lacking, a person should not be considered as having a valid history of disease, because other diseases may mimic mild atypical varicella.

- History of herpes zoster based on healthcare provider diagnosis.

Contraindications and Precautions to Vaccination

Varicella and MMRV Vaccines

Contraindications and precautions are similar for all varicella-containing vaccines. Persons with a severe allergic reaction (anaphylaxis) to a vaccine component or following a prior dose of vaccine should not receive varicella vaccine. Varicella, MMRV, and zoster vaccines all contain minute amounts of neomycin and hydrolyzed gelatin but do not contain egg protein or preservative.

Varicella-Containing Vaccines Contraindications and Precautions

- Severe allergic reaction to vaccine component or following a prior dose
- Immunosuppression
- Pregnancy
- Moderate or severe acute illness
- Recent blood product (except herpes zoster vaccine)

Persons with immunosuppression due to leukemia, lymphoma, generalized malignancy, immune deficiency disease, or immunosuppressive therapy should not be vaccinated with a varicella-containing vaccine. However, treatment with low-dose (less than 2 mg/kg/day), alternate-day, topical, replacement, or aerosolized steroid preparations is not a contraindication to vaccination. Persons whose immunosuppressive therapy with steroids has been discontinued for 1 month (3 months for chemotherapy) may be vaccinated.

Single-antigen varicella vaccine may be administered to persons with impaired humoral immunity (e.g., hypogammaglobulinemia). However, the blood products used to treat humoral immunodeficiency may interfere with the response to vaccination. Recommended spacing between administration of the blood product and receipt of varicella vaccine should be observed (see Chapter 2, General Recommendations on Immunization, for details).

Persons with moderate or severe cellular immunodeficiency resulting from infection with human immunodeficiency virus (HIV), including persons diagnosed with acquired immunodeficiency syndrome (AIDS) should not receive varicella vaccine. HIV-infected children with CD4 T-lymphocyte percentage of 15% or higher, and older children and adults with a CD4 count of 200 per microliter or higher may be considered for vaccination. These persons may receive MMR and single-antigen varicella vaccines, but should not receive MMRV.

Varicella Vaccine Use in Immunocompromised Persons

- MMRV not approved for use in persons with HIV infection
- Do not administer zoster vaccine to immunosuppressed persons

Women known to be pregnant or attempting to become pregnant should not receive a varicella-containing vaccine. To date, no adverse outcomes of pregnancy or in a fetus have been reported among women who inadvertently received varicella vaccine shortly before or during pregnancy. Although the manufacturer's package insert states otherwise, ACIP recommends that pregnancy be avoided for 1 month following receipt of varicella vaccine.

The ACIP recommends prenatal assessment and postpartum vaccination for varicella. Women should be assessed during a prenatal healthcare visit for evidence of varicella immunity. Upon completion or termination of pregnancy, women who do not have evidence of varicella immunity should receive the first dose of varicella vaccine before discharge from the healthcare facility. The second dose should be administered at least 4 weeks later at the postpartum or other healthcare visit. Standing orders are recommended for healthcare settings where completion or termination of pregnancy occurs to ensure administration of varicella vaccine.

Varicella Vaccination in Pregnancy Registry

800.986.8999

The manufacturer, in collaboration with CDC, has established a Varicella Vaccination in Pregnancy registry to monitor the maternal–fetal outcomes of pregnant women inadvertently given varicella vaccine. The telephone number for the Registry is 800-986-8999.

Vaccination of persons with moderate or severe acute illnesses should be postponed until the condition has improved. This precaution is intended to prevent complicating the management of an ill patient with a potential vaccine adverse event, such as fever. Minor illness, such as otitis media and upper respiratory infections, concurrent antibiotic therapy, and exposure or recovery from other illnesses are not contraindications to varicella vaccine. Although there is no evidence that either varicella or varicella vaccine exacerbates tuberculosis, vaccination is not recommended for persons known to have untreated active tuberculosis. Tuberculosis skin testing is not a prerequisite for varicella vaccination.

The effect of the administration of antibody-containing blood products (e.g., immune globulin, whole blood or packed red blood cells, or intravenous immune globulin) on the response to varicella vaccine virus is unknown. Because of the potential inhibition of the response to varicella vaccination by passively transferred antibodies, varicella or MMRV vaccine should not be administered for 3–11 months after receipt of antibody-containing blood products. ACIP recommends applying the same intervals used to separate antibody-containing products and MMR to varicella vaccine (see chapter 2, General Recommendations on Immunization, and Appendix A for additional details). Immune globulin should not be given for 3 weeks following vaccination unless the benefits exceed those

of the vaccine. In such cases, the vaccinees should either be revaccinated or tested for immunity at least 3 months later (depending on the antibody-containing product administered) and revaccinated if seronegative.

No adverse events following varicella vaccination related to the use of salicylates (e.g., aspirin) have been reported to date. However, the manufacturer recommends that vaccine recipients avoid the use of salicylates for 6 weeks after receiving varicella or MMRV vaccine because of the association between aspirin use and Reye syndrome following chickenpox.

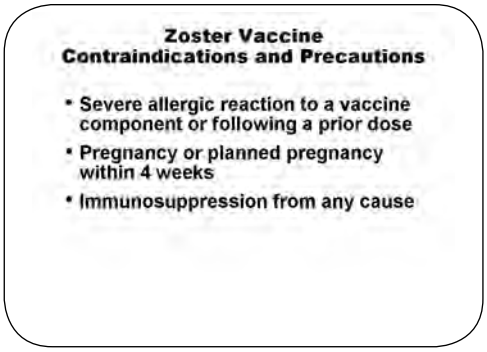
Zoster Vaccine

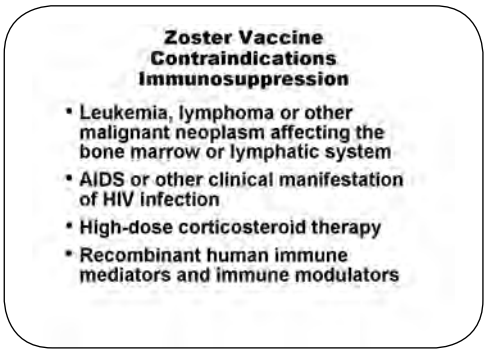
As with all vaccines, a severe allergic reaction to a vaccine component or following a prior dose is a contraindication to zoster vaccination. As with other live virus vaccines, pregnancy or planned pregnancy within 4 weeks and immunosuppression are contraindications to zoster vaccination.

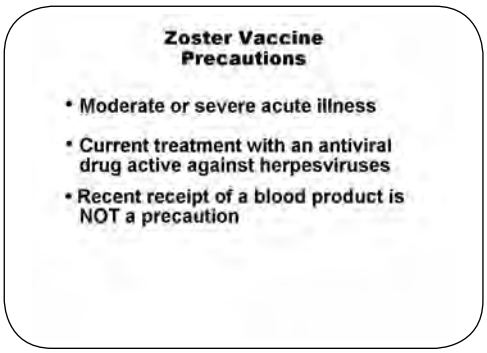
Zoster vaccine should not be administered to persons with primary or acquired immunodeficiency. This includes persons with leukemia, lymphomas, or other malignant neoplasms affecting the bone marrow or lymphatic system. The package insert implies that zoster vaccine should not be administered to anyone who has ever had leukemia or lymphoma. However, ACIP recommends that persons whose leukemia or lymphoma is in remission and who have not received chemotherapy or radiation for at least 3 months can be vaccinated. Other immunosuppressive conditions that contraindicate zoster vaccine include AIDS or other clinical manifestation of HIV. This includes CD4 T-lymphocyte values less than 200 per mm or less than 15% of total lymphocytes.

Persons receiving high-dose corticosteroid therapy should not be vaccinated. High dose is defined as 20 milligrams or more per day of prednisone or equivalent lasting two or more weeks. Zoster vaccination should be deferred for at least 1 month after discontinuation of therapy. As with other live viral vaccines, persons receiving lower doses of corticosteroids may be vaccinated. Topical, inhaled or intra-articular steroids, or long-term alternate-day treatment with low to moderate doses of short-acting systemic corticosteroids are not considered to be sufficiently immunosuppressive to contraindicate zoster vaccine.

Low doses of drugs used for the treatment of rheumatoid arthritis, inflammatory bowel disease, and other conditions, such as methotrexate, azathioprine, or 6-mercaptopurine, are also not considered sufficiently immunosuppressive to create safety concerns for zoster vaccine. Low-dose therapy with these drugs is NOT a contraindication for administration of zoster vaccine.







The experience of hematopoietic stem cell transplant recipients with varicella-containing vaccines, including zoster vaccine is limited. Physicians should assess the immune status of the recipient on a case-by-case basis to determine the relevant risks. If a decision is made to vaccinate with zoster vaccine, the vaccine should be administered at least 24 months after transplantation.

The safety and efficacy of zoster vaccine administered concurrently with recombinant human immune mediators and immune modulators (such as the anti–tumor necrosis factor agents adalimumab, infliximab, and etanercept) is not known. It is preferable to administer zoster vaccine before treatment with these drugs. If it is not possible to administer zoster vaccine to patients before initiation of treatment, physicians should assess the immune status of the recipient on a case-by-case basis to determine the relevant risks and benefits. Otherwise, vaccination with zoster vaccine should be deferred for at least 1 month after discontinuation of treatment.

As with all vaccines, moderate or severe acute illness is a precaution to vaccination. Current treatment with an antiviral drug active against herpesviruses, such as acyclovir, famciclovir, or valacyclovir, is a precaution to vaccination. These drugs can interfere with replication of the vaccine virus. Persons taking these drugs should discontinue them at least 24 hours before administration of zoster vaccine, and the drugs should not be taken for at least 14 days after vaccination.

Persons with a history of varicella are immune and generally maintain a high level of antibody to varicella zoster virus, a level comparable to that found in donated blood and antibody-containing blood products. Receiving an antibody-containing blood product will not change the amount of antibody in the person's blood. As a result, unlike most other live virus vaccines, recent receipt of a blood product is not a precaution for zoster vaccine. Zoster vaccine can be administered at any time before, concurrent with, or after receiving blood or other antibody-containing blood products.

Adverse Reactions Following Vaccination

Varicella Vaccine

The most common adverse reactions following varicella vaccine are local reactions, such as pain, soreness, erythema, and swelling. Based on information from the manufacturer's clinical trials of varicella vaccine, local reactions are reported by 19% of children and by 24% of adolescents and adults (33% following the second dose). These local adverse

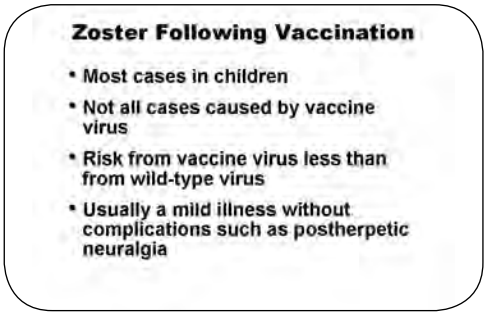
Varicella Vaccine Adverse Reactions

- Local reactions (pain, erythema)
  - —19% (children)
  - —24% (adolescents and adults)
- Generalized rash – 4%-6%
  - —may be maculopapular rather than vesicular
  - —average 5 lesions
- Systemic reactions not common
- Adverse reactions similar for MMRV

reactions are generally mild and self-limited. A varicella-like rash at injection site is reported by 3% of children and by 1% of adolescents and adults following the second dose. In both circumstances, a median of two lesions have been present. These lesions generally occur within 2 weeks, and are most commonly maculopapular rather than vesicular. A generalized varicella-like rash is reported by 4%–6% of recipients of varicella vaccine (1% after the second dose in adolescents and adults), with an average of five lesions. Most of these generalized rashes occur within 3 weeks and most are maculopapular.

Systemic reactions are not common. Fever within 42 days of vaccination is reported by 15% of children and 10% of adolescents and adults. The majority of these episodes of fever have been attributed to concurrent illness rather than to the vaccine.

Varicella vaccine is a live virus vaccine and may result in a latent infection, similar to that caused by wild varicella virus. Consequently, zoster caused by the vaccine virus has been reported, mostly among vaccinated children. Not all these cases have been confirmed as having been caused by vaccine virus. The risk of zoster following vaccination appears to be less than that following infection with wild-type virus. The majority of cases of zoster following vaccine have been mild and have not been associated with complications such as postherpetic neuralgia.

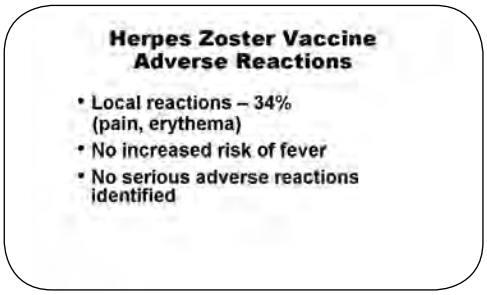


MMRV Vaccine

The clinical trial of MMRV compared events that occurred within 42 days of receiving either MMRV or MMR and varicella vaccine separately in different anatomic sites. The frequencies of local reactions and generalized varicella-like rash were similar to those described for varicella vaccine. A temperature of 102°F or higher within 42 days of vaccination was more common in the MMRV group (22%) than in the group that received MMR and varicella vaccine at different sites (15%). A measles-like rash also occurred more frequently in MMRV recipients (3%) than in the group receiving separate injections (2.1%). Both fever and measles-like rash usually occurred 5–12 days following vaccination.

Herpes Zoster Vaccine

In the largest clinical trial of zoster vaccine, local reactions (erythema, pain or tenderness, and swelling) were the most common adverse reaction reported by vaccine recipients (34%), and were reported more commonly than by placebo recipients (6%). A temperature of 101°F or higher within 42 days of vaccination occurred at a similar frequency among both vaccine (0.8%) and placebo (0.9%) recipients. No serious adverse reactions were identified during the trial.



Transmission of Varicella Vaccine Virus

Available data suggest that transmission of varicella vaccine virus is a rare event. Instances of suspected secondary transmission of vaccine virus have been reported, but in few instances has the secondary clinical illness been shown to be caused by vaccine virus. Several cases of suspected secondary transmission have been determined to have been caused by wild varicella virus. In studies of household contacts, several instances of asymptomatic seroconversion have been observed. It appears that transmission occurs mainly, and perhaps only, when the vaccinee develops a rash. If a vaccinated child develops a rash, it is recommended that close contact with persons who do not have evidence of varicella immunity and who are at high risk of complications of varicella, such as immunocompromised persons, be avoided until the rash has resolved.

Transmission of varicella vaccine virus from recipients of zoster vaccine has not been reported.

Vaccine Storage and Handling

Varicella-Containing Vaccine Storage and Handling

- Store frozen at 5°F (-15°C) or lower at all times
- Store diluent at room temperature or refrigerate
- Discard if not used within 30 minutes of reconstitution

Varicella vaccine is very fragile, and all vaccines that contain it must be handled with extreme care. To maintain potency, all varicella-containing vaccines must be stored frozen at an average temperature of 5°F (-15°C). Household freezers, including frost-free models, manufactured since the mid-1990s are acceptable for storage of these vaccines. Refrigerators with ice compartments that are not tightly enclosed or are enclosed with unsealed, uninsulated doors (i.e., small dormitory-style refrigerator/freezer combinations) are not capable of maintaining the required storage temperature. Regardless of the type of freezer, providers should check the adequacy of their freezer storage before obtaining vaccine by monitoring and verifying the temperature of their freezer.

The vaccine diluent should be stored separately at room temperature or in the refrigerator. The vaccine should be reconstituted according to the directions in the package insert and only with the diluent supplied (or with the diluent supplied for MMR vaccine), which does not contain preservative or other antiviral substances that might inactivate the vaccine virus. Once reconstituted, all varicella-containing vaccines must be used immediately to minimize loss of potency. The vaccine must be discarded if not used within 30 minutes of reconstitution.

Single-antigen varicella may be stored at refrigerator temperature for up to 72 hours. Vaccine stored in the refrigerator cannot be refrozen and must be discarded after 72 hours at this temperature.

Mishandled varicella vaccine should be clearly marked and replaced in the freezer separate from properly handled

vaccine. The manufacturer must be contacted for recommendations before any mishandled vaccine is used. The Merck Vaccine Division varicella information telephone number is 800-9VARIVAX (800-982-7482).

Zoster vaccine cannot be stored at refrigerator temperature at any time.

Because of the lability of varicella vaccine, transport of the vaccine from a central clinic or storage area to an off-site clinic can be difficult. If off-site transport is attempted, a properly insulated container should be used, the vaccine should be transported on dry ice, and the temperature should be monitored continuously, to ensure that the appropriate storage temperature is maintained (see Appendix C).

Varicella Vaccine Information

800-9VARIVAX

Varicella Zoster Immune Globulin

In 2004, the only U.S.-licensed manufacturer of varicella zoster immune globulin (VZIG) (Massachusetts Public Health Biologic Laboratories, Boston, Massachusetts) discontinued production of VZIG. The supply of the licensed VZIG product was depleted in early 2006. In February 2006, an investigational (not licensed) VZIG product, VariZIG (Cangene Corporation, Winnipeg, Canada) became available under an investigational new drug application (IND) submitted to the FDA. This product can be requested from the sole authorized U.S. distributor, FFF Enterprises (Temecula, California), for patients who have been exposed to varicella and who are at increased risk for severe disease and complications.

The investigational VariZIG, similar to licensed VZIG, is a purified human immune globulin preparation made from plasma containing high levels of anti-varicella antibodies (immunoglobulin class G [IgG]). Unlike the previous product, the investigational product is lyophilized. When properly reconstituted, VariZIG is approximately a 5% solution of IgG that can be administered intramuscularly. As with any product used under IND, patients must be informed of potential risks and benefits and must give informed consent before receiving the product.

Patients without evidence of immunity to varicella (i.e., without history of disease or age-appropriate vaccination) who are at high risk for severe disease and complications, who have been exposed to varicella, and from whom informed consent has been obtained, are eligible to receive the IND application product under an expanded access protocol. The patient groups recommended by ACIP to receive VariZIG include the following:

- Immunocompromised patients
- Neonates whose mothers have signs and symptoms of varicella around the time of delivery (i.e., 5 days before to 2 days after)

- Preterm infants born at 28 weeks gestation or later who are exposed during the neonatal period and whose mothers do not have evidence of immunity
- Preterm infants born earlier than 28 weeks' gestation or who weigh 1,000g or less at birth and were exposed during the neonatal period, regardless of maternal history of varicella disease or vaccination
- Pregnant women

Addition information concerning the acquisition and use of this product is available in the March 3, 2006, edition of *Morbidity and Mortality Weekly Report*, available at http://www.cdc.gov/*MMWR*/preview/*MMWR*html/mm5508a5.htm

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Anthrax

Anthrax is a zoonotic disease caused by the spore-forming bacterium *Bacillus anthracis*. The term anthrax is derived from the Greek word for coal, *anthrakis*, because of the black skin lesions characteristic of the disease. A disease that appears to have been anthrax was described in the biblical book of Exodus as the fifth plague in about 1490 BCE. Descriptions of anthrax affecting both animals and humans are found in early Indian and Greek writings. An epidemic of anthrax in 17th century Europe caused an estimated 60,000 human deaths. The contagious nature of anthrax was described in 1823. *Bacillus anthracis* was first described in 1849, and in 1876, Robert Koch definitively established a microbial origin for anthrax making this the first disease for which this was done. A live attenuated animal vaccine was developed and tested by Louis Pasteur in 1881. An improved animal vaccine containing a suspension of an avirulent, nonencapsulated live strain of *B. anthracis* was developed in 1939. The role of toxin in the pathogenesis of anthrax was demonstrated in 1954. A human vaccine composed of cell-free culture filtrate was developed in 1954, and in 1970 an improved cell-free vaccine was licensed in the United States. Anthrax was first used effectively as a bioterrorist agent in 2001.

Anthrax

- Zoonotic disease caused by *Bacillus anthracis*
- Described in biblical times
- First animal vaccine developed by Louis Pasteur in 1881
- Used for bioterrorism in 2001

Bacillus anthracis

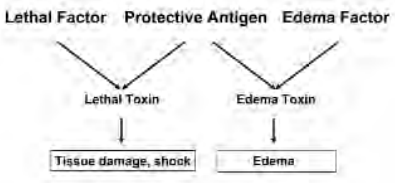
B. anthracis is a large aerobic, spore-forming, gram-positive bacillus that grows well on common culture media, such as blood agar. Stained *B. anthracis* from culture media appears as long parallel chains of organisms with square ends, referred to as "boxcars." *B. anthracis* spores can remain viable and infective in the soil for many years, even decades. During this time, they are a potential source of infection for grazing livestock, but they generally do not represent a direct infection risk for humans. Animals become infected when they ingest or inhale the spores while grazing. Humans can become infected with *B. anthracis* by skin contact, ingestion, or inhalation of *B. anthracis* spores originating from products of infected animals or from inhalation of spores from the environment. Spores can be inactivated with sufficient contact with paraformaldehyde vapor, 5% hypochlorite or phenol solution, or by autoclaving.

Bacillus anthracis

- Gram-positive aerobic bacteria
- Spores may remain viable in soil for years
- Spores inactivated by paraformaldehyde vapor, hypochlorite, phenol, or autoclave
- Toxins responsible for tissue damage and edema

Anthrax spores germinate when they enter an environment rich in amino acids, nucleosides, and glucose, such as the blood or tissues of an animal. The replicating bacteria produce at least three proteins—protective antigen (PA), lethal factor (LF), and edema factor (EF). These proteins combine to form two toxins known as lethal toxin and edema toxin. PA and LF form lethal toxin, a protease that is believed to be responsible for tissue damage, shock, and death, although

Anthrax Toxins

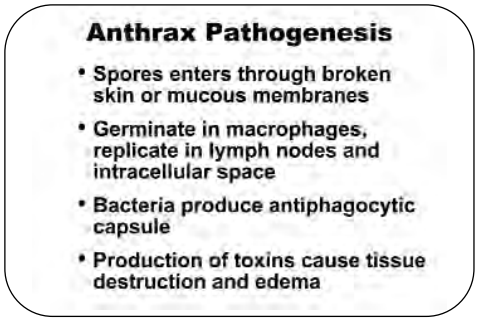


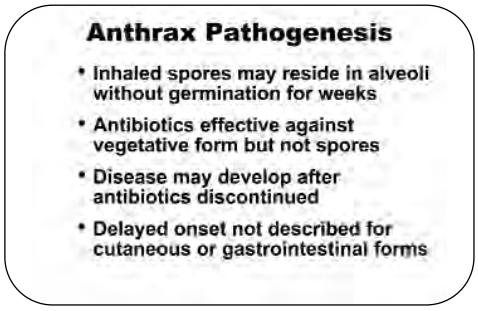
the mechanism is not clear. PA and EF form edema toxin, an adenylate cyclase that upsets controls on ion and water transport across cell membranes and causes extensive edema.

PA binds to receptors on mammalian cells and then binds with LF or EF. The toxin complexes are internalized to the endosome of the cell and then transported to the cytosol, where they exert their effect.

Pathogenesis

After wound inoculation or ingestion, *B. anthracis* spores are engulfed by macrophages, where they germinate. The vegetative bacterium produces a capsule that allows it to evade the immune system by resisting phagocytosis and protects the organism from lysis by cationic proteins in the serum. Lethal toxin and edema toxin are produced. If not contained, the bacteria can spread to draining lymph nodes and intracellular space, leading to further production of toxins. The toxins result in necrosis of lymphatic tissue, which leads to the release of large numbers of bacteria. Bacteremia may ensue and lead to overwhelming septicemia, widespread tissue destruction, organ failure, and death. In inhalation anthrax, spores are transported from the alveoli to the tracheobronchial and mediastinal lymph nodes. Lethal toxin and edema toxin are produced and cause tissue necrosis and extensive edema. Production of toxins leads to the massive hemorrhagic lymphadenitis and mediastinitis characteristic of inhalational disease.





Studies in animals indicate that inhaled spores may not immediately germinate within the alveoli but reside there potentially for weeks, perhaps months, until taken up by alveolar macrophages. Spores then germinate and begin replication within the macrophages and lymphatic tissue. Antibiotics are effective against germinating or vegetative *B. anthracis* but are not effective against the nonvegetative or spore form of the organism. Consequently, disease development can be prevented as long as a therapeutic level of antibiotics is maintained to kill germinating *B. anthracis* organisms. After discontinuation of antibiotics, if the remaining nongerminated spores are sufficiently numerous to evade or overwhelm the immune system when they germinate, disease will then develop. This phenomenon of delayed onset of disease is not recognized to occur with cutaneous or gastrointestinal exposures.

Clinical Features

There are three clinical forms of anthrax: cutaneous, gastrointestinal, and inhalation. **The symptoms and incubation period of human anthrax are determined by the route of transmission of the organism**.



Cutaneous Anthrax

Most (more than 95%) naturally occurring *B. anthracis* infections are cutaneous and occur when the bacterium enters a cut or abrasion on the skin (e.g., when handling *B. anthracis*–contaminated animals, animal products, or other objects). The reported incubation period for cutaneous anthrax ranges from 1 to 12 days. Skin infection begins as a small papule that may be pruritic, progresses to a vesicle in 1–2 days, and erodes leaving a necrotic ulcer (eschar) with a characteristic black center. Secondary vesicles around the primary lesions may develop. The lesion is usually painless. Other symptoms may include swelling of adjacent lymph nodes, fever, malaise, and headache. The diagnosis of cutaneous anthrax is suggested by the presence of the eschar, the presence of edema out of proportion to the size of the lesion, and the lack of pain during the initial phases of the infection. The case-fatality rate of cutaneous anthrax is 5%–20% without antibiotic treatment and less than 1% with antibiotic treatment.

Cutaneous Anthrax

- Incubation period 1-12 days
- Papule, then vesicle, then necrotic ulcer (eschar) with black center
- Usually painless
- Case-fatality:
  - —without antibiotics – 5%-20%
  - —with antibiotics – <1%

Gastrointestinal Anthrax

The intestinal form of anthrax usually occurs after eating contaminated meat. The incubation period for intestinal anthrax is believed to be 1–7 days. Involvement of the pharynx is characterized by lesions at the base of the tongue or tonsils, with sore throat, dysphagia, fever, and regional lymphadenopathy. Involvement of the lower intestine is characterized by acute inflammation of the bowel. Initial signs of nausea, loss of appetite, vomiting, and fever are followed by abdominal pain, vomiting of blood, and bloody diarrhea. The case-fatality rate of gastrointestinal anthrax is unknown but is estimated to be 25%–60%.

Gastrointestinal Anthrax

- Incubation period 1-7 days
- Pharyngeal involvement includes oropharyngeal ulcerations with cervical adenopathy and fever
- Intestinal involvement includes abdominal pain, fever, bloody vomiting or diarrhea
- Case-fatality estimated at 25%-60%

Inhalation Anthrax

Originally known as woolsorter's disease, inhalation anthrax results from inhalation of 8,000–50,000 spores of *B. anthracis*. This form of anthrax would be expected to be the most common following an intentional release of *B. anthracis*. The incubation period for inhalation anthrax for humans appears to be 1–7 days, but may be as long as 43 days. The median incubation period for the first 10 bioterrorism-related inhalation anthrax cases in 2001 was 4 days, with a range of 4–6 days. However, the incubation period for inhalation anthrax may be inversely related to the dose of *B. anthracis*. Data from studies of laboratory animals suggest that *B. anthracis* spores continue to vegetate in the host for several weeks after inhalation, and antibiotics can prolong the incubation period for developing disease.

Initial symptoms of inhalation anthrax can include a non-productive cough, myalgia, fatigue, and fever. Profound,

Inhalation Anthrax

- Incubation period: 1-7 days (range up to 43 days)
- Prodrome of cough, myalgia, fatigue, and fever
- Rapid deterioration with fever, dyspnea, cyanosis and shock, often with radiographic evidence of mediastinal widening
- Case-fatality:
  - —without antibiotic treatment – 85%- 97%
  - —with antibiotic treatment – 75% (45% in 2001)

often drenching sweat was a prominent feature of the first 10 bioterrorism-related cases in 2001. A brief period of improvement has been reported following the prodromal symptoms, but was not seen in the 2001 cases. Rapid deterioration then occurs, with high fever, dyspnea, cyanosis, and shock. Chest x-ray often shows pleural effusion and mediastinial widening due to lymphadenopathy. Meningitis, often hemorrhagic, occurs in up to half of patients with inhalation anthrax. Prior to the bioterrorist attacks in 2001, the case-fatality estimates without antibiotics were 85%–97%. With antibiotics, the case-fatality rate is estimated to be 75%. For inhalation anthrax cases in 2001, the case-fatality rate with intensive therapy was 45% (5 of 11 cases). Death sometimes occurs within hours of onset.

Initial symptoms of an **influenza-like illness (ILI)** could be similar to early symptoms of inhalation anthrax. ILI is a nonspecific respiratory illness characterized by fatigue, fever, cough, and other symptoms. Most cases of ILI are not caused by influenza but by other viruses, such as rhinovirus and adenovirus. **Nasal congestion and rhinorrhea (runny nose) are common with ILI, but not common with inhalation anthrax. Shortness of breath is common with inhalation anthrax but not common with ILI.** Most persons with inhalation anthrax have abnormalities on chest x-ray, whereas most persons with ILI do not have abnormal chest x-rays (although primary influenza pneumonia or secondary bacterial pneumonia may occur in persons with influenza).

Laboratory Diagnosis

Anthrax Laboratory Diagnosis

- Gram stain of clinical samples (skin lesion, blood, pleural fluid, CSF)
- Culture
- Adjunct Assays
  - –PCR
  - –serology (PA-based ELISA)
  - –immunohistochemistry

The diagnosis of cutaneous anthrax should be suspected by the characteristic painless, shallow ulcer with a black crust. Gram stain of vesicular fluid will reveal typical gram-positive bacteria. Diagnosis can be confirmed by culture. Gastrointestinal anthrax is difficult to diagnose because of its similarity to other severe gastrointestinal diseases. A history of ingesting potentially contaminated meat and presence of typical symptoms may be helpful. Diagnosis of inhalation anthrax can also be difficult. Mediastinal widening on chest x-ray is a useful clinical finding. The bacterial burden may be so great in advanced infection that bacteria are visible on Gram stain of unspun peripheral blood. Gram-positive bacteria may be present in other clinical specimens, such as pleural fluid, skin biopsy lesion material, oropharyngeal ulcers, or cerebrospinal fluid. Diagnosis is usually confirmed with a positive culture for *B. anthracis*. Standard blood cultures should show growth in 6–24 hours. Other laboratory tests that may assist in the diagnosis are polymerase chain reaction (PCR), which detects *B. anthracis* DNA in pleural fluid or blood, serology (PA-based ELISA), and tissue immunohistochemistry, in which tissue is stained with specific cell wall and capsular antibodies.

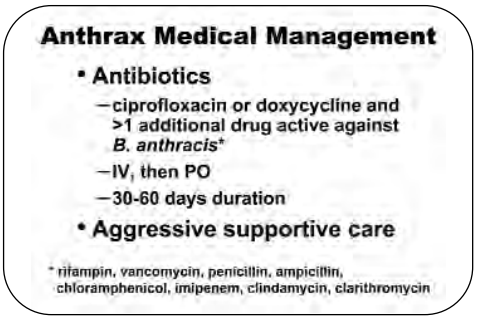
Medical Management

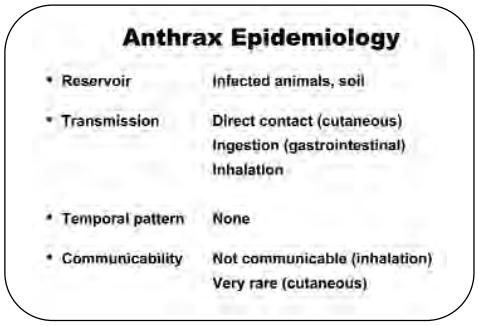
Antibiotics are the most important therapeutic intervention in any form of anthrax and should be started as soon as the disease is suspected. Naturally occurring strains of *B. anthracis* are typically sensitive to several antibiotics, including penicillin, tetracycline, and oral fluoroquinolones (ciprofloxacin and ofloxacin). *B. anthracis* produces a cephalosporinase that inhibits the antibacterial activity of cephalosporins such as ceftriaxone. Consequently, cephalosporins should not be used for treatment of anthrax. Naturally occurring *B. anthracis* may also be resistant to other commonly used antibiotics, such as sulfamethoxazole, trimethoprim, and aztreonam.

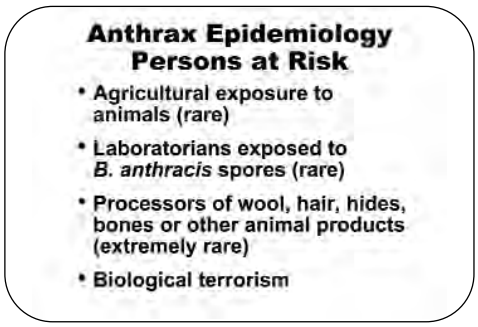
All patients with bioterrorism-related inhalation anthrax in 2001 received combination antimicrobial therapy with more than one agent active against *B. anthracis*. The survival rate among these patients was higher (55%) than in previous descriptions. The apparent improvement in survival suggests that the antibiotic combinations used in these patients may have therapeutic advantage compared with previous regimens. Limited data on treatment suggest that early intravenous treatment with a fluoroquinolone (e.g., ciprofloxacin) and at least one other active drug may improve survival. Treatment should initially be intravenous, then oral (PO) when clinically appropriate. Antibiotics should be continued for 30–60 days, or longer. In addition to antibiotics, aggressive supportive care, such as draining of pleural effusions, correction of electrolyte and acid-base disturbances, and early mechanical ventilation appear to increase the likelihood of survival for inhalation anthrax.

For cutaneous anthrax, ciprofloxacin or doxycycline is recommended as first-line therapy. Intravenous therapy with a multidrug regimen is recommended for cutaneous anthrax with signs of systemic involvement, for extensive edema, or for lesions on the head and neck. Cutaneous anthrax is typically treated for 7–10 days. However, in the setting of a bioterrorism attack, the risk for simultaneous aerosol exposure may be high. As a result, persons with cutaneous anthrax associated with a bioterrorism attack should be treated for 60 days. Even if promptly treated with appropriate antibiotics, cutaneous anthrax will continue to progress through the eschar phase.

The most current recommendations on treatment of anthrax can be found on the CDC Public Health Emergency Preparedness and Response website at http://www.bt.cdc.gov.







Epidemiology

Occurrence

Anthrax occurs worldwide and is most common in agricultural regions with inadequate control programs for anthrax in livestock. These regions include South and Central America, Southern and Eastern Europe, Asia, Africa, the Caribbean, and the Middle East. Prior to 2001, anthrax was very rare in the United States, with no human cases reported during 1993–1999.

Reservoir

The main reservoirs of anthrax are infected animals and soil. Anthrax spores are highly resistant to physical and chemical agents and persist in the environment for many years. The spores may remain dormant in certain types of soil for decades.

Transmission

The most common method of transmission of anthrax is through direct contact with an infected animal. *B. anthracis* may enter the body through a preexisting skin lesion or may be inadvertently introduced through an injury from a contaminated object. The result of this source of transmission is cutaneous anthrax. Vectors such as flies and vultures may mechanically spread the organism in some circumstances, but vectors are not believed to be important in human infection. Meat from an infected animal can transmit *B. anthracis* if the infected meat is eaten undercooked.

B. anthracis can also be transmitted by **inhalation of airborne or aerosolized spores**. In nature, *B. anthracis* spores are 2–6 microns in diameter. If aerosolized by industrial processing of contaminated products, or as a result of a bioterrorist attack, particles larger than 5 microns in diameter quickly fall from the atmosphere and bond to any surface. These particles are difficult to resuspend in the air, but may remain in the environment for years. Spores 2–5 microns in diameter behave as a gas and move through the environment without settling. Spores of this size are able to pass through the pores in paper, as occurred in mail processing facilities subsequent to the anthrax attacks in 2001. Particles smaller than 5 microns in diameter, if inhaled, are small enough to reach the lower respiratory tract and can lead to inhalation anthrax.

Naturally-occurring anthrax is extremely rare in the United States (see Secular Trends). Persons at risk of anthrax are primarily those who have contact with infected animals. However, although animal anthrax occurs in the United States, this mode of transmission is rare. Laboratory personnel

or other persons who come into contact with *B. anthracis* spores could be at increased risk, although only two laboratory-associated anthrax cases have been reported (both were inhalation anthrax). In the past, persons involved in processing wool, hair, hides, and/or bones from infected animals could be infected. However, improvements in animal husbandry and strict importation requirements for animal products have made this source of infection extremely rare. Exposure to *B. anthracis* through an effective bioterrorist attack occurred for the first time in 2001.

Temporal Pattern

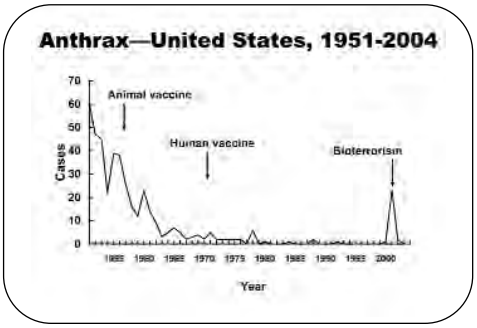
Anthrax may occur throughout the year. Animal-related cases occur primarily in the spring and summer.

Communicability

Persons with inhalation anthrax are not contagious. Human-to-human transmission of cutaneous anthrax has been reported but is very rare.

Secular Trends

Anthrax most commonly occurs in herbivores, which are infected by ingesting or inhaling spores from the soil. Humans are infected naturally following contact with anthrax-infected animals or anthrax-contaminated animal products. Estimation of the true incidence of human anthrax worldwide is difficult because reporting of anthrax cases is unreliable. The largest recent epidemic of human anthrax occurred in Zimbabwe during 1978–1980; 9,445 cases were reported, including 141 (1.5%) deaths.



In the United States, the annual incidence of human anthrax declined from approximately 130 cases annually in the early 1900s to no cases during 1993–1999. Most cases reported in the United States have been cutaneous. A single case of cutaneous anthrax was reported in 2000, and two cases were reported in 2002. During the 20th century, only 18 cases of inhalation anthrax were reported, the most recent in 1976. Gastrointestinal anthrax has not been reported in the United States.

Anthrax continues to be reported among domestic and wild animals in the United States. The incidence of anthrax in U.S. animals is not known. However, reports of animal infection have occurred in the Great Plains states from Texas to North Dakota.

Except for the single case in 2000 and two cases in 2002, all other cases of anthrax in the United States since 1993 were related to intentional exposure from a bioterrorist attack. Most infected persons were exposed in mail-sorting facilities

or had direct contact with a contaminated envelope. The source of the *B. anthracis* used in these attacks has not been determined.

Case Definition

A **confirmed case of anthrax** is defined as a clinically compatible case of cutaneous, respiratory, or gastrointestinal illness that is laboratory confirmed by isolation of *B. anthracis* from an affected tissue or site, or other laboratory evidence of *B. anthracis* infection based on at least two supportive laboratory tests. A **suspect case of anthrax** is a clinically compatible case of illness without isolation of *B. anthracis* and no alternative diagnosis, but with laboratory evidence of *B. anthracis* by one supportive laboratory test, or a clinically compatible case of anthrax epidemiologically linked to a confirmed environmental exposure, but without corroborative laboratory evidence of *B. anthracis* infection.

Any person suspected of having any type of anthrax must be reported immediately to the local or state health department.

Anthrax Vaccine

Anthrax Vaccines

- **1881** Pasteur develops first live attenuated veterinary vaccine for livestock
- **1939** Improved live veterinary vaccine
- **1954** First cell-free human vaccine
- **1970** Improved cell-free vaccine licensed

Louis Pasteur successfully attenuated *B. anthracis* and produced the first live attenuated bacterial vaccine for animals in 1881. An improved live vaccine containing an unencapsulated avirulent variant of *B. anthracis* (the Stern vaccine) was developed for livestock in 1939. This vaccine continues to be used as the principal veterinary vaccine in the Western Hemisphere. The use of livestock vaccines was associated with occasional death in the animal, and live vaccines were considered unsuitable for humans. In the early 20th century, filtrates of artificially cultivated *B. anthracis* were explored as potential vaccines. The first human culture filtrate vaccine was developed in 1954. This vaccine used alum as an adjuvant. It provided protection in monkeys, caused minimal reactivity and short-term adverse reactions in humans, and was used in the only efficacy study of human vaccination against anthrax in the United States. In the late 1950s the vaccine was improved through the selection of a *B. anthracis* strain that produced a higher fraction of protective antigen, the production of a protein-free medium, and the use of aluminum hydroxide rather than alum as the adjuvant. This vaccine—anthrax vaccine adsorbed (AVA)—was licensed for use in the United States in 1970.

Anthrax Vaccine

- Cell-free culture filtrate of toxigenic strain of *B. anthracis*
- Filtrate contains protective antigen (PA) and other cellular products
- Adsorbed to aluminum hydroxide as an adjuvant
- Contains small amounts of benzethonium chloride (preservative) and formaldehyde (stabilizer)

Characteristics

AVA is the only FDA-licensed human anthrax vaccine in the United States. It is prepared from a cell-free culture filtrate of a toxigenic, nonencapsulated strain of *B. anthracis*.

The vaccine does not contain dead or live bacteria. The filtrate contains a mix of cellular products and contains all three toxin components (LF, EF, and PA). The vaccine is adsorbed to aluminum hydroxide as an adjuvant. AVA contains no more that 0.83 mg aluminum per 0.5-mL dose, 0.0025% benzethonium chloride as a preservative, and 0.0037% formaldehyde as a stabilizer.

Immunogenicity and Vaccine Efficacy

The principal antigen responsible for producing immunity is PA. Approximately 83% of recipients of AVA develop detectable antibody to PA by 2 weeks after the first dose, and 91% after two or more doses. Approximately 95% of vaccinees seroconvert with a fourfold rise in anti-PA IgG titers after three doses. However, the precise correlation between antibody titer (or concentration) and protection against infection is not known with certainty.

Anthrax Vaccine Efficacy

- 95% seroconversion following 3 doses
- One controlled human trial using earlier vaccine
  - –92.5% efficacy (cutaneous and inhalation disease combined)
- Animal models suggest protection against inhalation anthrax
- Duration of immunity unknown

The only controlled clinical human trial of anthrax was performed among mill workers in 1955–1959 using the alum-precipitated vaccine (the PA-based precursor to the currently licensed AVA). In this controlled study, 379 employees received the vaccine, 414 received a placebo, and 340 received neither the vaccine nor the placebo. The study documented **a vaccine efficacy of 92.5% for protection against anthrax** (cutaneous and inhalation combined). During the study, an outbreak of inhalation anthrax occurred among the study participants. Overall, five cases of inhalation anthrax occurred in persons who were either placebo recipients or did not participate in the controlled part of the study. No cases occurred in anthrax vaccine recipients. No data are available regarding the efficacy of anthrax vaccine for persons younger than 18 years or older than 65 years of age.

Anthrax Vaccine Efficacy in Macaques

Year	Vaccine	Challenge	Time	Survival
1954	alum	50 x LD_{50}	16 d	7 of 7
1954	alum	100 x LD_{50}	16 d	4 of 4
			34 d	4 of 4
1956	alum	100 x LD_{50}	7 d	10 of 10
			1 yrs	10 of 10
			2 yrs	6 of 7
1995	alum. hyd.	200 x LD_{50}	8 wks	10 of 10
			38 wks	3 of 3
			100 wks	7 of 8
1995	alum. hyd.	200 x LD_{50}	12 wks	10 of 10

The protective efficacy of the alum-precipitated vaccine (the earlier form of the PA filtrate vaccine) and AVA has been demonstrated in several animal studies using different routes of spore exposure. Inhalation anthrax in macaque (Rhesus) monkeys is believed to best reflect human disease, and AVA has been shown to be protective for up to 100 weeks after pulmonary challenge with *B. anthracis*.

The duration of immunity in humans following vaccination with AVA is unknown. Data from animal studies suggest that the duration of efficacy after two inoculations might be 1–2 years.

Anthrax Vaccine Schedule

- Initial doses at 0, 2, and 4 weeks
- Additional doses at 6, 12, and 18 months
- Annual booster doses thereafter
- Alternative schedules being investigated

Vaccination Schedule and Use

Primary vaccination with AVA consists of three subcutaneous (SC) injections at 0, 2, and 4 weeks, followed by

doses at 6, 12, and 18 months. To maintain immunity, the manufacturer recommends an annual booster dose. The basis for the schedule of vaccinations at 0, 2, and 4 weeks, and 6, 12, and 18 months followed by annual boosters is not well defined.

As with other licensed vaccines, no data indicate that increasing the interval between doses adversely affects immunogenicity or safety. **Interruption of the vaccination schedule does not require restarting the entire series of anthrax vaccine or the addition of extra doses**.

Because of the complexity of a six-dose primary vaccination schedule and frequency of local injection-site reactions (see Adverse Reactions), studies are being conducted to assess the immunogenicity of schedules with a reduced number of doses and with intramuscular (IM) rather than subcutaneous administration. Preliminary results indicate that schedules using fewer doses at longer intervals, and IM rather than SC route, produce similar concentrations of antibody to PA. However, **no alternate schedule has yet been approved for use by the FDA**.

Anthrax Vaccine Preexposure Vaccination

- Persons working with production of quantities or concentrations of *B. anthracis* cultures
- Persons engaged in activities with a high potential for production of aerosols containing *B. anthracis*
- Persons with increased risk of exposure to intentional release of *B. anthracis* (e.g., certain military personnel)

Preexposure Vaccination

Routine preexposure vaccination with AVA is indicated for **persons engaged in work involving production of quantities or concentrations of *B. anthracis* cultures and in activities with a high potential for aerosol production**. Laboratory personnel using standard Biosafety Level 2 practices in routine processing of clinical samples are not at increased risk for exposure to *B. anthracis* spores. The risk for persons who come in contact in the workplace with imported animal hides, furs, bone meal, wool, animal hair, or bristles has been reduced by changes in industry standards and import restrictions. Routine preexposure vaccination is recommended only for persons in this group for whom these standards and restrictions are insufficient to prevent exposure to anthrax spores. Routine vaccination of veterinarians in the United States is not recommended because of the low incidence of animal cases. However, vaccination might be indicated for veterinarians and other persons handling potentially infected animals in areas with a high incidence of anthrax cases.

Preexposure vaccination may be indicated for certain military personnel and other select groups who may be exposed to an intentional release of *B. anthracis*. Preexposure vaccination is not currently recommended for emergency first responders, federal responders, medical practitioners, or private citizens.

Postexposure Vaccination

Limited data are available regarding the postexposure efficacy of AVA. **Studies in nonhuman primates indicate that postexposure vaccination alone is not protective**. However, studies have shown that **antibiotics in combination with postexposure vaccination are effective at preventing disease in animals after exposure to *B. anthracis* spores**. The current vaccine is approved by FDA only for preexposure vaccination. The optimal number of doses for postexposure prophylaxis use of the vaccine is not known. An estimated 83% of human vaccinees develop a vaccine-induced immune response after two doses of the vaccine, and more than 95% develop a fourfold rise in antibody titer after three doses. Although the precise correlation between antibody titer and protection against disease is not clear, these studies of postexposure vaccine regimens used in combination with antibiotics in nonhuman primates have consistently documented that one or two doses of vaccine were sufficient to prevent development of disease once antibiotics were discontinued.

Anthrax Vaccine Postexposure Vaccination

- No efficacy data for postexposure vaccination of humans
- Postexposure vaccination alone not effective in primates
- Combination of vaccine and antibiotics appears effective in animal model

Anthrax Postexposure Prophylaxis Vaccine Combined with Antibiotics

- Henderson, et al (1956): earlier PA-based vaccine
  - Methods: 5 days of penicillin compared to penicillin plus postexposure vaccination
  - Results: 9 of the 10 receiving just penicillin died, while all of the macaques receiving both penicillin and vaccine survived
- Friedlander et al (1993): aluminum hydroxide PA filtrate vaccine (current FDA-licensed vaccine)
  - Methods: 30 days of various antibiotics compared to 30 days of doxycycline plus postexposure vaccination
  - Results: 9 of the 10 animals in the doxycycline-alone arm survived, while all receiving doxycycline and vaccine survived

Adverse Reactions Following Vaccination

The most common adverse reactions following AVA are local reactions. In AVA prelicensure evaluations, minor local reactions (defined as erythema, edema, and induration less than 30 mm) occurred after 20% of vaccinations, moderate local reactions (edema and induration of 30–120 mm) occurred after 3% of vaccinations, and severe local reactions (edema or induration more than 120 mm) occurred after 1% of vaccinations. Local reactions usually occur within 24 hours and subside within 48 hours. Subcutaneous nodules occur at the injection site in 30%–50% of recipients and persist for several weeks. In multiple Department of Defense studies, systemic reactions (i.e., chills, muscle aches, malaise, or nausea) occurred in 5%–35% of vaccine recipients. Systemic reactions are usually mild and transient. Fever is not common following AVA. Severe (e.g., allergic) reactions are rare.

Anthrax Vaccine Adverse Reactions

• Local reactions	
– minor	20%-50%
– severe	1%
• Systemic symptoms	5%-35%
• Severe reactions	rare

Adverse reactions following anthrax vaccination have been assessed in several studies conducted by the Department of Defense in the context of the routine anthrax vaccination program. In one of these studies, 1.9% of vaccine recipients reported limitations in work performance or had been placed on limited duty due to a local reaction. Only 0.3% reported more than 1 day lost from work; 0.5% consulted a clinic for evaluation; and one person (0.02%) required hospitalization for an injection-site reaction. Adverse reactions were reported more commonly among women than among men.

No studies have documented occurrence of chronic diseases (e.g., cancer or infertility) following anthrax vaccination.

In an assessment of the safety of anthrax vaccine, the Institute of Medicine (IOM) noted that published studies reported no significant adverse effects of the vaccine, but the literature is limited to a few short-term studies. One published follow-up study of laboratory workers at Fort Detrick, Maryland, concluded that during the 25-year period following receipt of anthrax vaccine, the workers did not develop any unusual illnesses or unexplained symptoms associated with vaccination. The IOM found no evidence that people face an increased risk of experiencing life-threatening or permanently disabling adverse reactions immediately after receiving AVA, when compared with the general population. Nor did it find any convincing evidence that an elevated risk of developing long-term adverse health effects is associated with receiving AVA, although data are limited in this regard (as they are for all vaccines).

CDC has conducted two epidemiologic investigations of the health concerns of Persian Gulf War (PGW) veterans that examined a possible association with several factors, including anthrax vaccination. Current scientific evidence does not support an association between anthrax vaccine and PGW illnesses.

No data are available regarding the safety of anthrax vaccine for persons younger than 18 years and older than 65 years of age. Adverse reactions can occur in persons who must complete the anthrax vaccination series because of high risk of exposure or because of employment requirements. Several protocols have been developed to manage specific local and systemic adverse reactions (available at www.anthrax.osd.mil). However, these protocols have not been evaluated in randomized trials.

Contraindications And Precautions

As with all vaccines, AVA is **contraindicated for persons who have experienced a severe allergic (anaphylactic) reaction to a vaccine component or following a prior dose of AVA**. Anthrax vaccine is **contraindicated for persons who have recovered from anthrax** because of observations of more severe adverse reactions among recipients with a history of anthrax disease. **A moderate or severe acute illness** is a precaution, and vaccination should be postponed until recovery. This prevents superimposing the adverse reactions from the vaccine on the underlying illness or mistakenly attributing a manifestation of the underlying illness to the vaccine. Vaccine can be administered to persons who have mild illnesses with or without low-grade fever.

No studies have been published regarding use of anthrax vaccine among pregnant women. The vaccine is neither licensed nor recommended during pregnancy. Pregnant

Anthrax Vaccine
Contraindications and Precautions

- Severe allergic reaction to a vaccine component or following a prior dose
- Previous anthrax disease
- Moderate or severe acute illness

women should be vaccinated against anthrax only if the potential benefits of vaccination outweigh the potential risks to the fetus. No data suggest increased risk for side effects or temporally related adverse events associated with receipt of anthrax vaccine by breastfeeding women or breastfed children. AVA may be administered to an **immunosuppressed person** if necessary, but response to the vaccine may be suboptimal.

Postexposure Prophylaxis With Antibiotics

Ciprofloxacin, doxycycline, and procaine penicillin G, are approved by FDA for the treatment of anthrax and are considered the drugs of choice for the treatment of naturally occurring anthrax. In addition, ofloxacin has also demonstrated in vitro activity against *B. anthracis*. Although naturally occurring *B. anthracis* resistance to penicillin is rare, such resistance has been reported.

Anthrax Postexposure Antibiotic Prophylaxis

- Ciprofloxicin, doxycycline, and procaine penicillin G approved for postexposure prophylaxis after aerosol exposure to *B. anthracis*
- Due to latency of spores in lung, antibiotics should continue for 30-60 days or more
- Discontinue antibiotics after third dose of vaccine

Antibiotics are effective against the germinated form of *B. anthracis* but are not effective against the spore form of the organism. Following inhalation exposure, spores can survive in tissues for months without germination in nonhuman primates. This phenomenon of delayed vegetation of spores resulting in prolonged incubation periods has not been observed for routes of infection other than inhalation. In one study, macaques were exposed to four times the LD_{50} dose of anthrax spores (the dose of spores that will result in the death of 50% of the exposed animals). The proportion of spores that survived in the lung tissue was estimated to be 15%–20% at 42 days, 2% at 50 days, and less than 1% at 75 days. Spores have been detected in animals up to 100 days following exposure. Although the LD_{50} dose for humans is believed to be similar to that for nonhuman primates, the length of persistence of *B. anthracis* spores in human lung tissue is not known. The length of persistence probably depends on the dose inhaled. The prolonged incubation period reported in an outbreak of inhalation anthrax in the former Soviet Union suggests that lethal amounts of spores might have persisted up to 43 days after initial exposure.

Postexposure Prophylaxis Following Inhalation Exposure

Postexposure prophylaxis against *B. anthracis* with antibiotics is recommended following an aerosol exposure to *B. anthracis* spores. Such exposure might occur following an inadvertent exposure in a laboratory setting or a biological terrorist incident. Inhalation anthrax in humans has not been reported to result from contact with naturally occurring anthrax among animals. Currently, **ciprofloxacin, doxycycline, and procaine penicillin G** are approved by FDA for use as

Recommended Postexposure Prophylaxis to Prevent Inhalational Anthrax

	Initial Therapy	Duration
Adults (including pregnant women and immunocompromised)	Ciprofloxacin 500 mg PO BID OR Doxycycline 100 mg PO BID	60 days
Children	Ciprofloxacin 10-15 mg/kg PO Q 12 hrs* OR Doxycycline: >8 yrs and >45 kg: 100 mg PO BID ≥8 yrs and ≤45 kg: 2.2 mg/kg PO BID ≤8 yrs: 2.2 mg/kg PO BID	60 days

*Ciprofloxacin dose should not exceed 1 gram per day in children.

antibiotic prophylaxis for inhalation *B. anthracis* infection. Because of concern about the possible antibiotic resistance of *B. anthracis*, ciprofloxacin or doxycycline should be used initially for antibiotic prophylaxis until organism susceptibilities are known. Antibiotic chemoprophylaxis can be switched to penicillin VK or amoxicillin, particularly for children, once antibiotic susceptibilities are known and the organism is found to be penicillin susceptible with minimum inhibitory concentrations (MICs) attainable with oral therapy.

Because of the potential persistence of spores following an aerosol exposure, **antibiotic therapy should be continued for at least 60 days if used alone**. If vaccine is available, antibiotics can be discontinued after three doses of vaccine have been administered according to the standard schedule (0, 2, and 4 weeks). Although the shortened (3-dose) vaccine regimen has been effective when used in a postexposure regimen that includes antibiotics, the duration of protection after vaccination is not known. Therefore, if subsequent exposures occur, additional vaccinations might be required.

Postexposure Antibiotic Prophylaxis Following Cutaneous or Gastrointestinal Exposure

No controlled studies have been conducted in animals or humans to evaluate the use of antibiotics alone or in combination with vaccination following cutaneous or gastrointestinal exposure to *B. anthracis*. Cutaneous and rare gastrointestinal exposures of humans are possible following outbreaks of anthrax in livestock. In these situations, on the basis of pathophysiology, reported incubation periods, current expert clinical judgment, and lack of data, postexposure prophylaxis might consist of antibiotic therapy for 7–14 days. Antibiotics could include ciprofloxacin, ofloxacin, doxycycline, penicillin, or amoxicillin.

Vaccine Storage and Handling

AVA must be stored at 35°–46°F (2°–8°C). The vaccine should not be frozen. The manufacturer (Bioport Corporation, Lansing, Michigan [877-BIO-THRAX]) should be contacted for advice should the vaccine be exposed to freezing temperature or a prolonged period at room temperature.

Bioterrorism Preparedness

Research on anthrax as a biological weapon began more than 90 years ago. In 1999, at least 17 nations were believed to have offensive biological weapons programs; it is not known how many are working with anthrax. Iraq has acknowledged producing and weaponizing anthrax. One terrorist group, Aum Shinrikyo, dispersed aerosols of

Anthrax in Biological Terrorism

- *B. anthracis* considered likely biological terrorism threat
  - —aerosolized stable spore form
  - —human LD_{50} 8,000-40,000 spores (one deep breath at site of release)
  - —acute illness with high fatality rate

anthrax and botulism throughout Tokyo, Japan, on at least eight occasions. For unknown reasons the attacks failed to produce illness.

B. anthracis is considered one of the most likely biological warfare agents because of the ability of *B. anthracis* spores to be transmitted by the respiratory route, the high mortality of inhalation anthrax, and the greater stability of *B. anthracis* spores compared with other potential biological warfare agents. The World Health Organization estimates that 50 kg of *B. anthracis* released upwind of a population center of 500,000 could result in 95,000 deaths and 125,000 hospitalizations, far more deaths than predicted in any other scenario of agent release.

A total of 22 anthrax cases in four states and the District of Columbia occurred in October and November 2001 as a result of a series of bioterrorist attacks with *B. anthracis*. Eleven cases were inhalation anthrax, of which five were fatal. The organism was sent through the U.S. postal system. Nine of the cases of inhalation anthrax occurred in persons with direct exposure to an envelope containing *B. anthracis*. The envelopes contaminated several office buildings and mail processing centers. Cross-contamination of mail in the processing centers is suspected as the source of exposure in those cases without known direct exposure to a contaminated letter. Several thousand persons required postexposure antibiotic prophylaxis because of exposure to contaminated buildings. Information on the 2001 anthrax attacks, recommendations for management of anthrax infection and exposure, and information on bioterrorism preparedness is available on the CDC Public Health Emergency Preparedness and Response website at http://www.bt.cdc.gov.

Anthrax Bioterrorism Attacks–United States, 2001

- 22 cases (11 inhalation, 11 cutaneous) in 4 states and DC
- *B. anthracis* sent through U.S. mail
- Most exposures occurred in mail sorting facilities and sites where mail was opened

Bioterrorism Information

CDC Emergency Preparedness and Response Website

www.bt.cdc.gov

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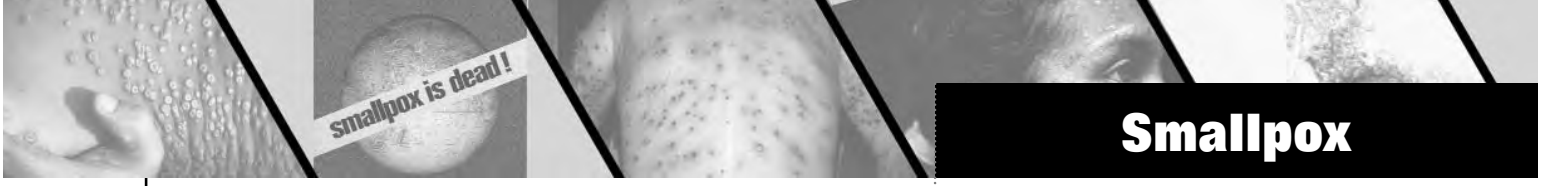
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Smallpox

Smallpox is an acute infectious disease caused by the variola virus. Smallpox is believed to have emerged in human populations about 10,000 BCE A description of smallpox first appeared in a Chinese text in the 4th century. The name variola was first used during the 6th century and is a derivative of the Latin *varius*, meaning spotted, or *varus*, meaning pimple. The first efforts to prevent smallpox occurred in China and India sometime before the year 1000 and involved intentional inoculation of a susceptible person with pustular or scab material from a person with smallpox. The term smallpox was first used in Europe in the 15th century to distinguish variola from the great pox (syphilis). In 1796, Edward Jenner demonstrated that smallpox could be prevented by inoculating a person with material from a cowpox lesion; this led to the first smallpox vaccine. The last case of smallpox in the United States was reported in Texas in 1949. In 1966, the World Health Organization initiated an intensified global smallpox eradication program. The last indigenous case of smallpox on earth occurred in Somalia in October 1977. The World Health Assembly officially certified the global eradication of smallpox in May 1980.

Smallpox

- First described in Chinese text in 4th century
- Vaccine developed in late 18th century
- Last case in U.S. in 1949
- Last indigenous case on earth in 1977

Variola and Other Orthopoxviruses

Smallpox is caused by variola virus. Variola virus belongs to the genus *Orthopoxvirus*, family Poxviridae. Poxviruses are large brick-shaped viruses with a double stranded DNA genome. They are different from most other DNA viruses in that they replicate in the cytoplasm of the cell rather than in the nucleus. To do this, they produce a variety of proteins not produced by other DNA viruses (e.g., herpesvirus). Four orthopoxviruses are known to infect humans: variola, vaccinia, cowpox, and monkeypox. Variola virus infects only humans in nature, although primates and other animals have been infected in a laboratory. Vaccinia, cowpox, and monkeypox viruses can infect both humans and other animals in nature.

In laboratory experiments, 90% of aerosolized variola virus is inactivated within 24 hours. In the presence of ultraviolet light, this percentage would be even greater. In temperate climates, crusts from the skin lesions from smallpox patients, in which the virus is contained in a fibrin matrix, can retain viable virus for several years when held at room temperature. The virus survives longer at low temperature and humidity than at higher temperature or humidity. All poxviruses are rapidly inactivated by exposure to ultraviolet light, and chemical disinfectants such as bleach or Lysol®.

Some persons infected with variola major virus have particularly severe illnesses. This suggests that there could be differences

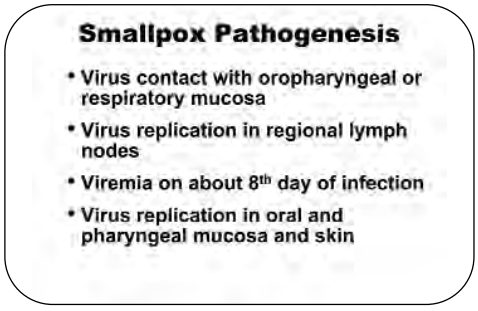
Variola Virus

- *Orthopoxvirus*
- Infects only humans in nature
- May remain viable in crusts for years at room temperature
- Rapidly inactivated by UV light, chemical disinfectants

in the virulence of strains of the virus. However, no laboratory test has been devised that correlates virus strains with virulence in humans. Physiologic factors in the host are probably the more important determinant of severity of the illness.

Smallpox vaccine contains vaccinia virus, not variola virus. Vaccinia is rarely isolated from animals outside the laboratory. There are multiple strains of vaccinia virus that have different levels of virulence for humans and animals. Vaccinia virus can also be genetically engineered to accept DNA and express other antigens, and has been used as a vector in laboratory experiments. Cowpox virus was probably the virus that Edward Jenner originally used as a vaccine for smallpox. The virus has many natural hosts, including cows, rodents, cats, elephants, and is found in nature primarily in Europe. Monkeypox was first found in monkeys and later in other animals such as rats, rabbits, and squirrels. It was reported in humans for the first time in 1970. It is found primarily in western and central Africa, although a cluster of monkeypox cases occurred in the United States in 2003 and was associated with pet prairie dogs from Africa.

Pathogenesis



Variola virus infection is initiated when the virus comes into contact with the oropharyngeal or respiratory mucosa of a susceptible person. The virus then multiplies in regional lymph nodes. An asymptomatic viremia develops 3 or 4 days after infection, which is followed by further virus replication, probably in the bone marrow, spleen, and lymphatics. A second viremia begins about 8–10 days after infection and is followed by the first symptoms of illness (prodromal stage), fever and toxemia. The virus localizes in small blood vessels of the dermis and in the oral and pharyngeal mucosa. In the skin, this results in the characteristic maculopapular rash, which evolves into vesicles, then pustules.

Clinical Features



Two clinical forms of smallpox have been described. While both forms are caused by variola virus, they are caused by different strains of the virus distinguishable by specific biologic properties (such as growth characteristics in cell culture and DNA structure). **Variola major** is the severe form of smallpox, with a more extensive rash, higher fever, and a greater degree of prostration. **Variola major** has a case-fatality rate of 30% or more. The last case of variola major occurred in Bangladesh in 1975. Variola minor was first described in South Africa and the United States in the late 19th century. Variola minor is a much less severe disease, with a case-fatality rate of 1% or less. Variola minor was endemic in some countries of Europe and of North and

South America and in many parts of Africa. The last case of variola minor occurred in Somalia in October 1977, and was the last case of indigenous smallpox on earth.

There are **four principal clinical presentations of variola major**, based on the Rao classification (1972). The relative vigor of the immune response to the infection probably determined the clinical presentation of the infection. The classification is based on the nature and evolution of the lesions: **ordinary** (most frequent), **modified** (mild and occurring in previously vaccinated persons), **flat**, and **hemorrhagic**. Flat and hemorrhagic smallpox are severe, uncommon forms and are usually fatal. In addition, variola sine eruptione (smallpox without rash) is a febrile illness occurring after the usual incubation period. It is seen generally in vaccinated persons and can be confirmed only by antibody studies or, rarely, by virus isolation. Subclinical (asymptomatic) infections with variola virus also occurred, but are not believed to be common.

Clinical Presentations of Variola Major

- Ordinary (≥90% of cases in unvaccinated persons)
- Modified (mild; occurs in previously vaccinated persons)
- Flat (uncommon; usually fatal)
- Hemorrhagic (uncommon; usually fatal)

The **incubation period** of smallpox averages 12 days, with a range of 7 to 17 days. During this period the patient is well. The **prodrome** or preeruptive stage of the illness then starts abruptly, with fever (usually 101°–104°F [38.3°–40°C)]), malaise, headache, muscle pain, prostration, and often nausea and vomiting and backache. The person usually appears quite ill. The prodrome usually lasts 2–4 days. The person is not infectious until the end of the prodrome, when lesions develop in the mouth.

Smallpox Prodrome

- Incubation period 12 days (range 7-17 days)
- Prodrome
  - —abrupt onset of fever ≥101°F
  - —malaise, headache, muscle pain, nausea, vomiting, backache
  - —lasts 2-4 days
  - —not infectious until lesions develop in mouth

Ordinary Smallpox

Ninety percent or more of smallpox cases among unvaccinated persons are of the ordinary type. The prodromal stage varies in severity. By the third or fourth day of illness, the temperature usually falls and the patient feels somewhat better. At this point the rash appears. The rash appears first as an **enanthem**—minute red spots on the tongue and oral and pharyngeal mucosa—about 24 hours before the appearance of rash on the skin. Lesions in the mouth and pharynx enlarge and ulcerate quickly, releasing large amounts of virus into the saliva about the time the cutaneous rash first becomes visible. Virus titers in saliva are highest during the first week of illness, corresponding with the period during which patients are most infectious.

Smallpox Rash

- Enanthem (mucous membrane lesions) appears approx. 24 hours before skin rash
- Minute red spots on the tongue and oral/pharyngeal mucosa
- Lesions enlarge and ulcerate quickly
- Virus titers in saliva highest during first week of illness

The **exanthem** (skin rash) usually appears 2–4 days after the onset of fever as a few macules (known as "herald spots") on the face, particularly on the forehead. Lesions then appear on the proximal portions of the extremities, then spread to the distal extremities and the trunk. Usually the rash appears on all parts of the body within 24 hours.

Smallpox Rash

- Exanthem (skin rash) appears 2-4 days after onset of fever
- First appears as macules, usually on the face
- Lesions appear on proximal extremities, spread to distal extremities and trunk

Smallpox Rash Evolution

Stage	Days after Rash Onset
Macules	0-1
Papules	2-3
Vesicles	3-5
Pustules	6-12
Crusts	13-20
All crusts separated	21-28

By the second or third day of the rash, the macules become raised papules. By the third or fourth day the lesions become vesicular, containing first an opalescent fluid, which then becomes opaque and turbid within 24–48 hours. The skin lesions of smallpox typically are surrounded by a faint erythematous halo. The distended vesicles often have a central depression or dimple of varying size, referred to as "**umbilication**." Umbilication often persists into the pustular stage, but as the lesion progresses it usually becomes flattened because of adsorption of fluid. Umbilication is less common in other vesicular or pustular rash illnesses, particularly in varicella.

By the sixth or seventh day, all the skin lesions are pustules. Between 7 and 10 days the pustules mature and reach their maximum size. The pustules are sharply raised, typically round, tense, and firm to the touch. **The pustules are deeply embedded in the dermis, giving them the feel of a small bead in the skin**. Fluid is slowly absorbed from the pustules, and by the end of the second week the pustules begin to form a crust. During the third week the crusts separate, leaving depigmented skin and, frequently, pitted scars. Fever usually rises again by the seventh or eighth day of the illness and continues to remain high throughout the vesicular and pustular stages, until crusts have formed over all the lesions.

Smallpox Rash

- Vesicles often have a central depression ("umbilication")
- Pustules raised, round, firm to the touch, deeply embedded in the skin
- Lesions in any one part of the body are in same stage of development
- Most dense on face and distal extremities (centrifugal distribution)
- Lesions on palms and soles (≥50% of cases)

The rash usually develops as a single crop. Consequently, **lesions in a particular part of the body are at about the same stage of development, although they may be different sizes**. The distribution of the rash is centrifugal: most dense on the face; more dense on the extremities than on the trunk; and on the extremities, more dense on the distal parts than on the proximal. The palms of the hands and soles of the feet are involved in the majority of cases.

In general, the severity of the clinical picture parallels the extent of the rash. In some cases, the pustular skin lesions on the extensor surfaces of the extremities and face are so numerous they became confluent. Patients with confluent smallpox often remain febrile and toxic even after scabs have formed over all the lesions. In one case series, the case-fatality rate in confluent smallpox was 62%.

Modified Smallpox

- Occurs in previously vaccinated persons
- Prodrome may be less severe
- No fever during evolution of rash
- Skin lesions evolve more quickly
- Rarely fatal
- More easily confused with chickenpox

Modified Smallpox

Modified smallpox refers to the character of the eruption and the rapidity of its development. This form of smallpox occurs mostly in previously vaccinated patients. The prodromal illness occurs but may be less severe than in ordinary-type smallpox. Fever during evolution of the rash is usually absent. The skin lesions tend to evolve more quickly, are more superficial, and may not show the uniformity

characteristic of more typical smallpox. The lesions are often few in number, but even when they are numerous, or even confluent, they usually evolve rapidly. Modified smallpox is rarely, if ever, fatal. This form of variola major is more easily confused with chickenpox.

Flat (Malignant) Smallpox

Flat-type smallpox is so called because the lesions remain almost flush with the skin at the time when raised vesicles form in ordinary-type smallpox. It is not known with certainty why some persons develop this type of disease. In a large series of persons hospitalized with smallpox in India, flat-type smallpox accounted for 5%–10% of cases, and the majority (72%) were in children. The prodrome is severe and lasts 3–4 days. Constitutional symptoms are severe and continue after the appearance of the rash. The fever remains elevated throughout and the patient has severe toxemic symptoms. The rash on the tongue and palate is usually extensive. The skin lesions mature very slowly. By the seventh or eighth day the lesions are flat and appear to be buried in the skin. Unlike ordinary-type smallpox, the vesicles contain very little fluid and do not appear umbilicated. The lesions are soft and velvety to the touch, and may contain hemorrhages. Respiratory complications are common. The prognosis for flat-type smallpox is grave and most cases are fatal.

Flat Smallpox

- Severe prodrome
- Fever remains elevated throughout course of illness
- Extensive enanthem
- Skin lesions soft and flat, contain little fluid
- Most cases fatal

Hemorrhagic Smallpox

Hemorrhagic smallpox is a severe and uncommon form of smallpox that is accompanied by extensive bleeding into the skin, mucous membranes, and gastrointestinal tract. In the large Indian series, hemorrhagic disease occurred in about 2% of hospitalized patients; the majority of cases were among adults, and pregnant women appear to be at increased risk. The prodromal stage, which can be prolonged, is characterized by fever, intense headache and backache, restlessness, a dusky flush or sometimes pallor of the face, extreme prostration, and toxicity. There is little or no remission of fever throughout the illness. Hemorrhagic manifestations can occur early or late in the course of the illness. In the early, or fulminating, form, hemorrhagic manifestations appear on the second or third day as subconjunctival bleeding, bleeding from the mouth or gums and other mucous membranes, petechiae in the skin, epistaxis, and hematuria. Death often occurs suddenly between the fifth and seventh days of illness, when only a few insignificant maculopapular cutaneous lesions are present. In patients who survive for 8–10 days the hemorrhages appear in the early eruptive period, and the rash is flat and does not progress beyond the vesicular stage.

Hemorrhagic Smallpox

- Prolonged severe prodrome
- Fever remains elevated throughout course of illness
- Early or late hemorrhagic signs
- Bleeding into skin, mucous membranes, GI tract
- Usually fatal

Variola Sine Eruptione and Subclinical Infection

Febrile illness sometimes occurs among vaccinated contacts of smallpox patients, with the sudden onset of temperature of about 102°F (39°C), headache and sometimes backache. The attack often subsides within 48 hours and the temperature returns to normal. Although these symptoms could be caused by other infections, laboratory investigation may show a significant increase in variola antibody following such an attack. There is evidence of true subclinical infection with variola major virus (i.e., serologic evidence of infection with no symptoms), typically in recently vaccinated household contacts of smallpox patients. Persons with subclinical infections have not been shown to transmit the infection to contacts.

Complications

Secondary bacterial infection of the skin is a relatively uncommon complication of smallpox. When this occurs, the fever usually remains elevated. **Arthritis** occurs in up to 2% of cases, most commonly in children. **Respiratory complications** (e.g., bronchitis, pneumonitis, or pneumonia) sometimes develop on about the eighth day of the illness and can be either viral or bacterial in origin. **Encephalitis** occasionally occurs and is indistinguishable from the acute perivascular demylination observed as a complication of infection due to vaccinia, measles, or varicella.

Smallpox Complications

- Bacterial infection of skin lesions
- Arthritis
- Respiratory
- Encephalitis
- Death
  - —30% overall for ordinary smallpox
  - —40%-50% for children <1 year
  - —>90% for flat and hemorrhagic smallpox

In fatal cases, **death** usually occurs between the tenth and sixteenth days of the illness. The cause of death from smallpox is not clear, but the infection is now known to involve multiple organs. Circulating immune complexes, overwhelming viremia, or an uncontrolled immune response may be contributing factors. The overall case-fatality rate for ordinary-type smallpox is about 30%. However, the fatality rate for children younger than 1 year of age is 40%–50%. The fatality rate for flat-type and hemorrhagic smallpox is 90% or greater. The case-fatality rate for variola minor is 1% or less.

Sequelae of smallpox include scarring, which is most common on the face, blindness resulting from corneal ulceration and scarring, and limb deformities due to arthritis and osteomyelitis. There is no evidence of chronic or recurrent infection with variola virus.

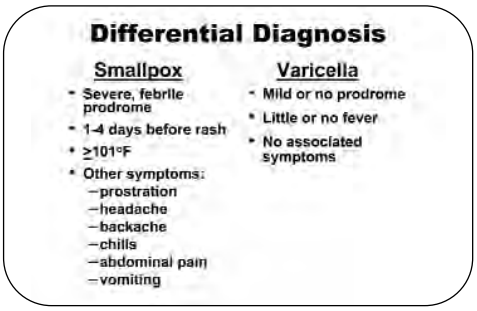
Differential Diagnosis

The disease that most closely resembles smallpox is varicella (chickenpox). **The most important differentiating feature between smallpox and varicella, as well as other rash illnesses, is the presence of a prodrome with fever and**

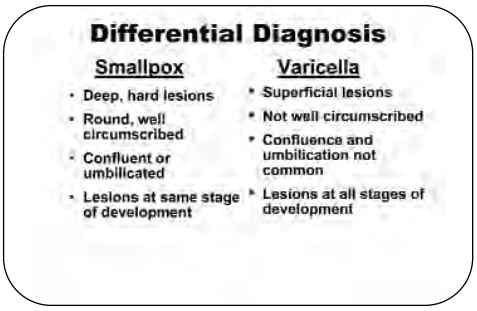
Differential Diagnosis

The most important differentiating feature between smallpox and other rash illnesses is the presence of fever before rash onset

other symptoms before rash onset. A person with smallpox will have a severe, febrile prodrome that begins 1–4 days before the onset of the rash. The fever is high, usually 102°–104°F (3.8.8°–40°C), but always at least 101°F (38.3°C). Most children with varicella have a short, mild prodrome or no prodrome at all before onset of the rash and have little or no fever before rash onset. Adults, who may develop more severe varicella, are more likely to have fever or other symptoms before rash onset. **If there is no history of a febrile prodrome, smallpox is not likely**. In addition to fever, the prodrome of smallpox is associated with one or more additional symptoms, such as prostration, headache, backache, chills, abdominal pain or vomiting. Patients are frequently too ill to engage in normal activities and typically confine themselves to bed.



Another important differentiating feature of smallpox and varicella is the appearance, evolution, and distribution of the rash. Although there may be some similarity in the appearance of the lesions, particularly early after rash onset, classic smallpox looks very different from varicella. Smallpox lesions are deep in the dermis and feel hard to the touch, described as feeling like a pea under the skin. They are round and well circumscribed. As they evolve, they may become confluent or umbilicated. The varicella rash is superficial, and the lesions appear to be delicate and not as well circumscribed. Confluence and umbilication are uncommon in varicella. Smallpox rash lesions appear in a single crop, and lesions on any part of the body are in the same stage of development. Lesions are more dense on the extremities than on the trunk and often involve the palms and soles (i.e., centrifugal distribution). In contrast, the rash of varicella appears in several crops, so papules, vesicles, and crusts are seen simultaneously on the same part of the body and new lesions continue to appear for several days. Lesions are typically more dense on the trunk than on the extremities. In severe cases of varicella, rash distribution may not be a useful differentiating feature and rash may occur everywhere on the body, including the palms and soles.



For the first 2–3 days, the smallpox rash is maculopapular. At this stage of the illness smallpox could be confused with other febrile illnesses with maculopapular rash, such as measles, rubella, and other evolving vesicular rashes including varicella

Other common conditions that might be confused with smallpox are summarized in the table below. As the United States re-institutes smallpox vaccination, at least in limited groups, generalized vesicular rashes (generalized vaccinia and eczema vaccinatum) caused by vaccinia vaccine adverse reactions could be seen among persons with a history of recent smallpox vaccination or contact close with a vaccinee.

In addition there are exceedingly rare causes of smallpox-like rash, such as rickettsial pox and monkeypox. A small percentage of smallpox cases present as hemorrhagic smallpox or a flat-type rash. Both variants are highly lethal. Hemorrhagic smallpox can be mistaken for meningococcemia.

Common Conditions that Might be Confused with Smallpox

Condition	Clinical Clues
Varicella (primary infection with varicella-zoster virus)	Most common in children <10 years; children usually do not have a viral prodrome
Disseminated herpes zoster	Immunocompromised or elderly persons; rash looks like varicella, usually begins in dermatomal distribution
Impetigo *(Streptococcus pyogenes, Staphylococcus aureus)*	Honey-colored crusted plaques with bullae are classic but may begin as vesicles; regional not disseminated rash; patients generally not ill
Drug eruptions	Exposure to medications; rash often generalized
Contact dermatitis	Itching; contact with possible allergens; rash often localized in pattern suggesting external contact
Erythema multiforme minor	Target, "bull's eye", or iris lesions; often follows recurrent herpes simplex virus infections; may involve hands & feet (including palms & soles)
Erythema multiforme (incl. Stevens–Johnson Syndrome)	Major form involves mucous membranes & conjunctivae; may be target lesions or vesicles
Enteroviral infection esp. Hand, Foot and Mouth disease	Summer & fall; fever & mild pharyngitis 1-2 days before rash onset; lesions initially maculopapular but evolve into whitish-grey tender, flat often oval vesicles; peripheral distribution (hands, feet, mouth, or disseminated)
Disseminated herpes simplex	Lesions indistinguishable from varicella; immunocompromised host
Scabies; insect bites (incl. fleas)	Itching is a major symptom; patient is not febrile & is otherwise well
Molluscum contagiosum	May disseminate in immunosuppressed persons

CDC has developed criteria that can be used to evaluate suspected smallpox cases and to categorize patients into high, moderate or low risk for smallpox. There are three major and five minor smallpox criteria:

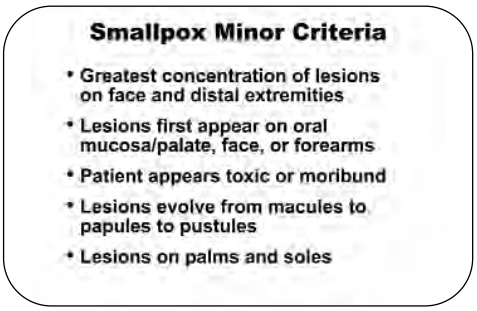
Major criteria

1. The patient has had a febrile prodrome (temperature 101°F [38.3°C]) or higher) 1–4 days before rash onset and at least one of the following systemic complaints: prostration, headache, backache, chills, vomiting or abdominal pain.
2. Rash lesions are deep in the skin, firm or hard to the touch, round and well circumscribed, and may become umbilicated or confluent as they evolve.
3. On any one part of the body all the lesions are in the same stage of development (i.e., all are vesicles or all are pustules).

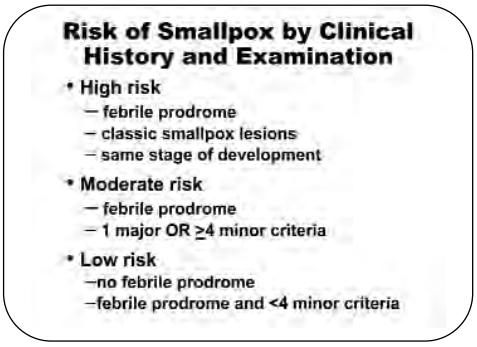


Minor criteria

1. The distribution of the rash is centrifugal (i.e., the greatest concentration of lesions is on the face and distal extremities with relative sparing of the trunk).
2. The first lesions of the rash appear on the oral mucosa or palate, or on the face or forearms.
3. The patient appears toxic or moribund.
4. Lesions have progressed slowly (i.e., the individual lesions evolved from macules to papules to pustules, each stage lasting 1–2 days).
5. Lesions are present on the palms or soles.



A person is considered at **high risk** for smallpox if he or she meets all three major criteria. Immediate action should be taken to make sure that contact precautions and respiratory isolation are implemented. These patients should be reported to local and/or state health authorities immediately. Obtain digital photographs if possible, and consult with dermatology and/or infectious disease experts. Following such consultation, if the patient is still considered to be at high risk, the state health department will immediately report the case to CDC and arrangements will be made for laboratory testing for smallpox virus.

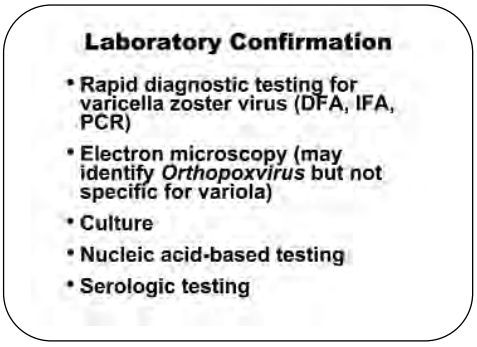


A person considered at **moderate risk for** smallpox must have a febrile prodrome and either one other major criterion or four or more minor criteria. These patients should be isolated and be evaluated urgently to determine the cause of the illness. Persons classified as high or moderate risk should be seen in consultation with a specialist in infectious diseases and/or dermatology whenever possible. Any person who did not have a febrile prodrome is considered at **low risk**, as are persons who had a febrile prodrome and fewer than four minor criteria. These patients should be managed as clinically indicated.

A case investigation worksheet and a poster that includes the rash illness algorithm, and information on differential diagnosis is available from the CDC smallpox website at http://www.bt.cdc.gov/agent/smallpox/

Laboratory and Pathology Diagnosis

If a case is classified as high risk after evaluation using the algorithm, it fits the clinical case definition for smallpox and therefore should be considered a probable smallpox case until smallpox virus laboratory results are completed. For such a case, do not perform other laboratory testing for other diagnoses.



Currently, laboratory procedures for isolation of variola virus in clinical specimens should be done only by CDC in

Atlanta. If the patient's clinical characteristics indicate a high risk for smallpox, the state health department should be contacted immediately. The diagnosis of an *Orthopoxvirus* infection can be made rapidly by electron microscopic examination of pustular fluid or scabs. Orthopox generic polymerase chain reaction (PCR) tests are available but do not distinguish between vaccinia, variola and other poxvirus infections. Differentiation of orthopoxviruses is made by nucleic acid–based testing, such as PCR. Serologic tests have also been developed to assist in the diagnosis of acute *Orthopoxvirus* infection, and direct antigen detection tests for variola virus are under development.

For a patient who meets the criteria for moderate risk, **the most important laboratory procedure is rapid diagnostic testing for varicella zoster virus (VZV)**. Laboratory testing should be done in consultation with an infectious disease or dermatology specialist. Smallpox virus testing is not indicated for cases that do not meet the clinical case definition. In the absence of smallpox (disease prevalence of zero), the predictive value of a positive laboratory test is extremely low (close to zero). Limiting requests for smallpox testing to cases that fit the clinical case definition will minimize the risks of a false-positive laboratory result, which would have extremely serious consequences.

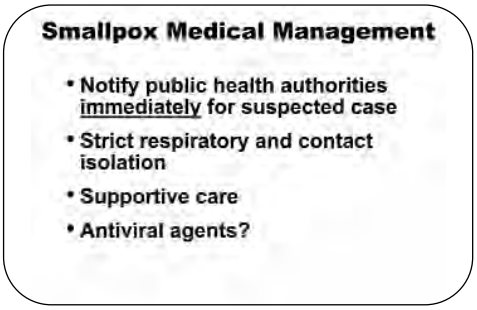
Since varicella was the most common disease confused with smallpox in the past and the most common diagnosis in smallpox false alarms in the immediate posteradication era, rapid VZV diagnostic tests are important for evaluation of suspected smallpox cases. A variety of rapid methods are available for detecting VZV in clinical material. The most useful is direct fluorescent antibody (DFA). This method detects VZV directly in cells using anti-VZV antibody conjugated to fluorescein dye. DFA is very sensitive and specific but is critically dependent on careful collection of material from a lesion. Detection of VZV DNA by PCR testing of vesicular fluid or scabs can also be used for rapid detection of VZV in clinical material. Real time PCR assays take 4–6 hours to perform. Virus particles consistent with VZV can be detected using electron microscopy. Rapid diagnostic testing for VZV is generally available in at least one facility (private laboratories, academic hospital centers) in all large cities and in some local and in all state health department facilities. Other testing should be done as clinically indicated and may include testing for herpes simplex viruses (HSV), enteroviruses and syphilis.

Tzanck smear, although not diagnostic of VZV infection, is a rapid and easily performed test in hospitals with a pathology laboratory and is frequently available at the local level. A positive Tzanck smear confirms an alphaherpesvirus infection (either VZV or HSV).

Skin biopsies, if clinically indicated, can assist with a diagnosis on the basis of histopathology or can be confirmatory if immunohistochemistry tests are available.

Medical Management

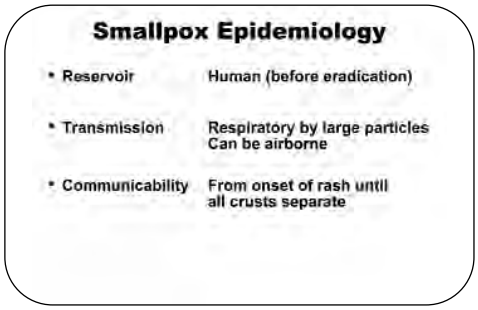
A suspected case of smallpox is a public health and medical emergency. Any person whose clinical characteristics meet the clinical case definition for smallpox must be isolated and reported immediately to the local and/or state health department.

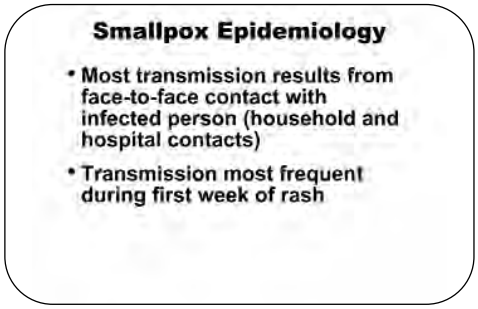


Strict respiratory and contact isolation of confirmed or suspected smallpox patients is critical to limit the exposure to the virus. Smallpox patients are infectious until all crusts have separated. Although droplet spread is the major mode of person-to-person smallpox transmission, airborne transmission through fine particle aerosol can occur. Therefore, airborne precautions using a negative air pressure room with high-efficiency particulate air filtration should be initiated immediately for hospitalized high-risk or confirmed smallpox patients. This is the same isolation precaution that is taken for other infectious diseases with respiratory transmission, such as varicella.

All personnel who have contact with a patient with suspected or confirmed smallpox should use appropriate protective equipment. This includes properly fitted respirators (masks) of N95 quality or higher. In addition, personnel should use disposable gloves, gowns and shoe covers for all contact with patients. This precaution is to prevent inadvertent transmission of variola virus from clothing or other contaminated items to susceptible persons. Personnel should remove and correctly dispose of all protective clothing before contact with other people. Reusable bedding and clothing can be autoclaved or laundered in hot water with bleach to inactivate the virus. Persons such as laundry handlers, housekeepers, and laboratory personnel, who come into contact with materials potentially contaminated with smallpox virus, should use appropriate protective equipment. If a case of smallpox is confirmed, these personnel should be vaccinated before handling contaminated materials.

Medical management of a person with smallpox is primarily supportive. No antiviral drug is currently approved by the Food and Drug Administration for the treatment of smallpox. Recent studies suggest that the antiviral drug cidofovir might be useful as a therapeutic agent. However, the drug must be administered intravenously and can cause serious renal toxicity. Cidofovir administered for the treatment of smallpox would be an off-label use. Antiviral therapy with cidofovir or other drugs subsequently found to have antivariola activity might be considered but should be used under an investigational new drug (IND) protocol and by an infectious diseases specialist.





Epidemiology

Reservoir

Although animals can be infected with variola in laboratory conditions, humans are the only natural host. There is no chronic carrier state and no known animal reservoir. Since the early 1980s (i.e., following global smallpox eradication), the only known locations of variola virus are at CDC in Atlanta and at the State Research Center of Virology and Biotechnology in Koltsovo, Russia.

Transmission

Transmission of smallpox occurs through inhalation of airborne variola virus, usually droplets expressed from the oral, nasal, or pharyngeal mucosa of an infected person. Most transmission results from direct face-to-face contact with an infected person, usually within a distance of 6 feet, or from physical contact with a person with smallpox or with contaminated articles. Although variola virus could remain viable for years in dried crusts of skin lesions, transmission from crusts is uncommon, probably because virus is enmeshed in a fibrin matrix.

Communicability

A person infected with variola virus is not infectious during the incubation period or the first day or two of the prodromal stage of the illness. The patient becomes infectious with the first appearance of the rash, which is often accompanied by lesions in the mouth and pharynx. The virus can be transmitted throughout the course of the illness (i.e., until all crusts separate). Transmission is most frequent during the first week of the rash, while most skin lesions are intact (i.e., vesicular or pustular). Virus is present in material draining from ruptured pustules and in crusts for a longer period, but infection from this source appears to be less frequent. In general, persons with a severe rash and involvement of the mouth and pharynx, and those with a cough are more infectious than those with a slight rash. Secondary attack rates among household members are generally 50%–60%.

Natural transmission of smallpox in a population is relatively slow. There is an interval of 2 to 3 weeks between each generation of cases. Smallpox generally spreads less widely and less rapidly than does varicella or measles, probably because transmission of variola virus does not occur until the onset of rash and generally requires close face-to-face contact for spread. At the time of rash onset, most patients are already confined to bed because of the high fever and toxemia of the prodromal stage of the illness. However, persons with severe prodromal illness may seek medical

attention; therefore, hospitals are a frequent source of infection because of transmission from hospitalized persons with unrecognized cases.

Secondary cases of smallpox are usually limited to those who come in contact with the infected person in the household or hospital. During the global eradication program, the chain of transmission of smallpox was interrupted by isolating smallpox patients in a setting in which they had contact only with adequately vaccinated or previously infected persons. This limited the next potential generation of cases to the household and close contacts of the index patient or patients. Contacts were identified and immediately vaccinated. Contacts who became ill were also isolated to establish a barrier to further transmission. This strategy was found to be effective even if community vaccination levels were low.

Temporal Pattern

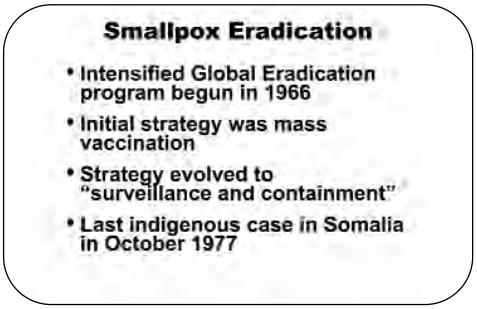
In temperate areas, the seasonality of smallpox was similar to that of measles and varicella, with incidence highest during the winter and spring. In tropical areas, seasonal variation was less evident and the disease was present throughout the year.

Secular Trends

The last case of smallpox in the United States was reported in 1949. In the early 1950s, an estimated 50 million cases of smallpox occurred worldwide each year. Ten to 15 million cases occurred in 1966, when the disease had already been eliminated in 80% of the world.

Smallpox Eradication

The intensified global smallpox eradication program began in 1966. The initial campaign was based on a twofold strategy: 1) mass vaccination campaigns in each country, using vaccine of ensured potency and stability, that would reach at least 80% of the population; and 2) development of surveillance systems to detect and contain cases and outbreaks. The program had to surmount numerous problems, including lack of organization in national health services, epidemic smallpox among refugees fleeing areas stricken by civil war and famine, shortages of funds and vaccine, and a host of other problems posed by difficult terrain, climate, and cultural beliefs. In addition, it was soon learned that even when 80% of the population was vaccinated, smallpox often persisted. Soon after the program began, it became apparent that by isolating persons with smallpox and vaccinating their contacts, outbreaks could be more rapidly contained, even in areas where vaccination coverage was low. This strategy was called **surveillance and containment**, and it became the key element in the global eradication program.



Although setbacks occurred, the surveillance and containment strategy was an enormous success. The last case of smallpox in Brazil was reported in 1971, and Indonesia's last case occurred in 1972. India, Pakistan and Bangladesh, with a population at that time of more than 700 million, were a particular challenge. But with intensive house-to-house searches and strict containment, the last case of variola major—the most deadly type of smallpox—occurred in Bangladesh in October 1975.

By the end of 1975, smallpox persisted only in the Horn of Africa. Conditions were very difficult in Ethiopia and Somalia, where there were few roads. Civil war, famine, and refugees made the task even more difficult. An intensive surveillance and containment and vaccination program was undertaken in the spring and summer of 1977. As a result, the world's last person with indigenous smallpox was a hospital cook in Merka, Somalia, on October 26, 1977. Searches for additional cases continued in Africa for more than 2 years, during which time thousands of rash illnesses were investigated. None proved to be smallpox.

The last cases of smallpox on earth occurred in an outbreak of 2 cases (one of which was fatal) in Birmingham, England in 1978. This outbreak occurred because variola virus was carried by the ventilation system from a research laboratory to an office one floor above the laboratory. In 1980 the World Health Assembly certified the global eradication of smallpox and recommended that all countries cease vaccination. The World Health Organization also recommended that all laboratories either destroy their remaining stocks of variola virus or transfer them to one of two WHO reference laboratories, the Institute of Viral Preparations in Moscow or CDC in Atlanta. All laboratories were believed to have complied with this request.

Case Definition

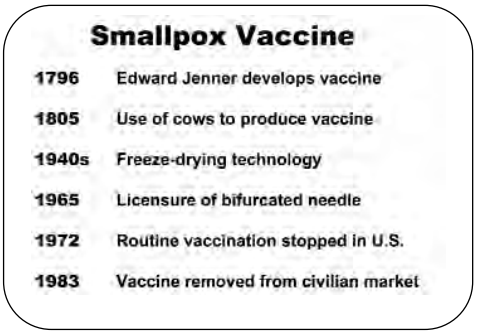
A clinical case of smallpox is defined as an illness with acute onset of fever (101°F [38.3°C] or higher) followed by a rash characterized by firm, deep-seated vesicles or pustules in the same stage of development without other apparent cause.

This case definition will not detect an atypical presentation of smallpox such as hemorrhagic or flat-type disease. In addition, given the extremely low likelihood of smallpox occurring, the case definition provides a high level of specificity (i.e., vesicular rash illness) rather than a high level of sensitivity (i.e., maculopapular rash illness). In the event of a smallpox outbreak, the case definition would be modified to increase sensitivity.

Smallpox (Vaccinia) Vaccine

The first attempts to prevent smallpox were in China and India before the year 1000 century, and involved either nasal insufflation of powdered smallpox scabs, or scratching material from a smallpox lesion into the skin. This procedure was known as variolation and, if successful, produced lasting immunity to smallpox. However, because the person was infected with variola virus, a severe infection could result, and the person could transmit smallpox to others.

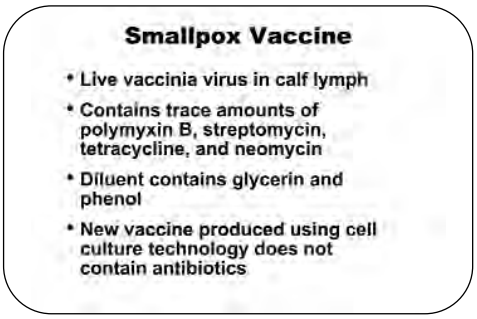
In 1796 **Edward Jenner**, a doctor in rural England, discovered that immunity to smallpox could be produced by inoculating a person with material from a cowpox lesion. Cowpox is a poxvirus in the same family as variola. Jenner called the material used for inoculation vaccine, from the root word *vacca*, which is Latin for cow. The procedure was much safer than variolation, and did not involve a risk of smallpox transmission. Vaccination to prevent smallpox was soon practiced all over the world.



At some time during the 19th century, the cowpox virus used for smallpox vaccination was replaced by vaccinia virus. Vaccinia is in the same family as cowpox and variola but is genetically distinct from both. The origin of vaccinia virus and how it came to be in the vaccine are not known.

Characteristics

The smallpox vaccine currently available in the United States (Dryvax, produced by Wyeth) is a **live virus preparation of infectious vaccinia virus**. Smallpox vaccine does not contain smallpox (variola) virus. The current vaccine was prepared in the early 1980s from calf lymph with a seed virus derived from the New York City Board of Health (NYCBOH) strain of vaccinia virus. The vaccine is provided as a lyophylized (freeze-dried) powder in a 100-dose vial and contains the antibiotics polymyxin B, streptomycin, tetracycline and neomycin. The diluent used to reconstitute the vaccine is 50% glycerin and contains a small amount of phenol as a preservative.



Approximately 15 million doses of vaccine are available now in the United States. Testing has shown that existing supplies of vaccine could be diluted by a 1:5 ratio and still remain as effective and safe as full-strength vaccine. An additional 85 million doses of vaccine based on the NYCBOH strain have been found to be immunogenic at 1:5 or 1:10 dilution. This could potentially provide an additional 850 million doses.

The vaccine is administered by using a multiple puncture technique with a special bifurcated needle. Detailed information concerning reconstitution and administration

of smallpox vaccine are available on the CDC smallpox website at http://www.cdc.gov/smallpox.

Response to Smallpox Vaccination

- Neutralizing antibody develops
  - 10 days after primary vaccination
  - 7 days after revaccination
- >95% of primary vaccinees develop detectable neutralizing antibody
- Antibody persists >10 years

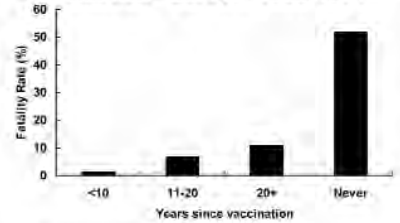
Smallpox Vaccine Efficacy

- Clinical efficacy estimated in household contact studies
- 91%-97% reduction in cases among contacts with vaccination scar
- Studies did not consider time since vaccination or potency of vaccine

Duration of Immunity Following Smallpox Vaccination

- High level of protection (~100%) for up to 5 years following vaccination
- Substantial but waning immunity for ≥10 years
- Reduction in disease severity among previously vaccinated persons

Smallpox Fatality Rate by Time Since Vaccination—Europe, 1950-1971*



*Mack TM. *J Infect Dis* 1972;125:161-8

Immunogenicity and Vaccine Efficacy

Neutralizing antibodies induced by vaccinia vaccine are genus-specific and cross-protective for other orthopoxviruses (e.g., monkeypox, cowpox, and variola viruses). Neutralizing antibodies are detectable 10 days after primary vaccination, and 7 days after revaccination. Although the level of antibody that protects against smallpox infection is unknown, after percutaneous administration of a standard dose of vaccinia vaccine, more than 95% of primary vaccinees (i.e., persons receiving their first dose of vaccine) will develop neutralizing or hemagglutination inhibition antibody at a titer of higher than 1:10. Neutralizing antibody titers of higher than 1:10 persist in 75% of persons for 10 years after receiving second doses and up to 30 years after receiving three doses of vaccine.

The efficacy of smallpox vaccine has never been measured precisely in controlled trials. However, protection has been determined in studies of persons exposed to a smallpox patient in their household. These studies indicated a 91%–97% reduction in smallpox among contacts with a vaccination scar compared with contacts without a scar. However, these studies did not always consider the time since vaccination or potency of vaccine, so they may underestimate protection.

Epidemiologic studies demonstrated that a high level of protection (nearly 100%) against smallpox persists for up to 5 years after primary vaccination, and substantial but waning immunity for 10 years or more. Antibody levels after revaccination can remain high longer, conferring a greater period of immunity than occurs after primary vaccination alone. Although smallpox vaccination received in the remote past may not completely protect against smallpox, vaccinated persons appear to have less severe disease. Studies of smallpox cases imported into Europe in the 1950s and 1960s demonstrated fewer fatalities among vaccinated persons compared with those who were unvaccinated. The fatality rate among persons vaccinated less than 10 years before exposure was 1.3%; it was 7% among those vaccinated 11 to 20 years prior, and 11% among those vaccinated 20 or more years prior to infection. In contrast, 52% of unvaccinated persons died.

Smallpox vaccination also provides protection if administered after an exposure to smallpox. **Postexposure efficacy** has been estimated in household contact studies in Pakistan and India. These studies indicate that rates of secondary cases in

households were up to 91% lower than rates among unvaccinated persons. The lowest secondary attack rates occurred in persons vaccinated less than 7 days after exposure. In these studies, smallpox was generally less severe (i.e., modified type) in persons who received postexposure vaccination.

Following vaccination, vaccinia virus replicates in the basal cells of the epidermis, resulting in the development of a lesion at the site of vaccination. A papule develops at the inoculation site 3–4 days after primary vaccination. Approximately 7 days following primary vaccination, a vesicle (a blister containing clear fluid) surrounded by erythema (a "Jennerian vesicle") forms at the site. The vesicle becomes pustular by 7–11 days after vaccination. Maximum erythema occurs 8–12 days after vaccination. The erythema then subsides, the pustule dries, and a crust develops 2–3 weeks after vaccination. In the third week, the crust separates, leaving a permanent scar at the vaccination site. This response to vaccination is called a **major reaction**, and indicates that virus replication has taken place and vaccination was successful. **A person is considered protected with the development of a major reaction at the vaccination site**. A revaccinated person often develops a skin reaction similar to that after primary vaccination, but the lesion progresses faster than after primary vaccination.

Some persons do not develop a typical skin lesion after vaccination. All responses other than major reactions are referred to as **equivocal**. There are several possible causes of equivocal reactions. The person may be sufficiently immune to suppress viral replication or may be allergic to a component of the vaccine, leading to a hypersensitivity reaction at the site. An equivocal reaction could also be caused by insufficiently potent vaccine or incorrect administration technique. In general, a person who has an equivocal response to vaccination should be revaccinated using vaccine from another vial if possible. More information on interpretation of response to vaccination is available in the ACIP recommendations for smallpox vaccine, available at http://www.cdc.gov/mmwr/PDF/rr/rr5010.pdf.

Live vaccinia virus is present at the vaccination site beginning 3 to 4 days after vaccination and remains until the crust separates from the skin. Since the developing vaccinia lesion usually itches, care must be taken to avoid scratching, then touching other parts of the body, such as the eye, or other people. This could transfer the vaccine virus to these sites or individuals. Washing hands immediately after touching the vaccination site or dressing is very important in preventing this type of transmission.

Postexposure Vaccine Efficacy

- Secondary attack rates reduced up to 91% compared to unvaccinated contacts
- Lowest disease rates among persons vaccinated <7 days after exposure
- Disease generally less severe (modified-type) in persons receiving postexposure vaccination

Clinical Response to Smallpox Vaccination*

Symptom/Sign	Time after vac
Papule	3-4 days
Vesicle	5-6 days
Pustule	7-11 days
Maximum erythema	8-12 days
Scab	14 days
Scab separation	21 days

*typical response in a nonimmune person

Clinical Response to Smallpox Vaccination

- Major (primary) reaction
  - –indicates viral replication has occurred and vaccination was successful
  - –considered to be protected with the development of a major reaction
- Equivocal reaction
  - –indicates immune suppression of viral replication, allergic reaction without production of immunity, incorrect vaccination technique, or impotent vaccine
  - –revaccinate immediately

Evolution of U.S. Smallpox Vaccine Recommendations

- **1972** Discontinue routine vaccination
- **1976** Discontinue vaccination of HCWs
- **1980** Vaccine recommended for lab workers
- **1990** Discontinue vaccination of military
- **1991** Consider vaccine for HCWs exposed to recombinant vaccinia
- **2001** Bioterrorism guidelines
- **2002** Smallpox Response Teams

Smallpox Vaccine
Indications in Nonemergency Situations

- Laboratory workers who handle cultures or animals infected with non-highly attenuated vaccinia
- Laboratory workers exposed to other Orthopoxviruses that infect humans
- Consider for other healthcare workers with contact with contaminated material
- Public health, hospital, and other personnel who may need to respond to a smallpox case or outbreak
- Persons who vaccinate others

Smallpox Vaccine
Indications in Emergency Situations*

- Persons exposed to initial release
- Close contact with confirmed or suspected case
- Direct care or transportation of confirmed or suspected case-patient
- Laboratory personnel
- Persons with risk of contact with infectious materials from patient
- Other groups as recommended by public health authorities

*following confirmation of a case of smallpox

Vaccination Schedule and Use

Routine childhood smallpox vaccination was discontinued in the United States in 1972. Routine vaccination of healthcare workers was discontinued in 1976, and among military recruits in 1990. In 1980, smallpox vaccine was recommended for laboratory workers who were at occupational risk for exposure to vaccinia or other orthopoxviruses. In 1991, the Advisory Committee on Immunization Practices recommended that other healthcare workers who could be exposed to vaccinia or recombinant vaccinia be considered for vaccination. Guidelines for use of smallpox vaccine in the event of an intentional release of smallpox virus were first published in 2001.

For routine nonemergency use (i.e., in the absence of smallpox disease) **vaccination is recommended for laboratory workers who directly handle cultures or animals contaminated or infected with non–highly attenuated vaccinia viruses** (e.g., the NYCBOH, Temple of Heaven, Copenhagen, or Lister vaccinia strains), and recombinant vaccinia viruses derived from non–highly attenuated vaccinia strains. Vaccination is also recommended for laboratory workers exposed to other orthopoxviruses that infect humans (e.g., monkeypox or cowpox). Vaccination can be considered for other healthcare workers who come into contact with materials such as dressings that may be contaminated with vaccinia or recombinant vaccinia. This could occur, for example, in the course of a clinical trial in which humans were administered vaccines containing recombinant vaccinia viruses. **Vaccination is also recommended for public health, hospital, and other personnel who may need to respond to a smallpox case or outbreak, and for persons who administer the vaccine to others**.

In the event of an intentional release of variola virus, vaccination would be recommended for those exposed to the initial release, contacts of persons with smallpox, and others at risk of exposure. Persons at risk of exposure would include those involved in the direct medical or public health evaluation, care or transportation of confirmed or suspected smallpox patients; laboratory personnel who collect or process clinical specimens from confirmed or suspected smallpox patients; persons who may have contact with infectious materials, such as those responsible for medical waste disposal, linen disposal or disinfection, and room disinfection in a facility where smallpox patients are present; and other groups (e.g., medical, law enforcement, emergency response, or military personnel) as recommended by public health authorities.

The **schedule** for smallpox vaccine is one successful dose (i.e., a dose that results in a major reaction at the vaccination site). In routine circumstances the vaccine should not be

administered to persons younger than 18 years of age. In an emergency (postrelease) situation, there would be no age limit for vaccination of persons exposed to a person with confirmed smallpox.

Persons with occupational exposure to non–highly attenuated vaccinia viruses, recombinant viruses derived from non–highly attenuated vaccinia viruses, or other nonvariola orthopoxviruses should be revaccinated at least every 10 years. To ensure an increased level of protection against more virulent nonvariola orthopoxviruses (e.g., monkeypox), empiric revaccination every 3 years can be considered.

Smallpox Vaccine

- **Schedule**
  - –1 successful dose
- **Revaccination**
  - –10 years (non-highly attenuated vaccinia and recombinants)
  - –3 years (more virulent Orthopoxviruses)

Adverse Reactions Following Vaccination

A vesicular or pustular skin lesion at the site of inoculation indicates a successful vaccination, or "take." In a 2002 study of old and new vaccines given to unvaccinated adults, the average size of the pustule at 2 weeks after vaccination was 12 millimeters. The average size of erythema surrounding the pustule was 16–24 millimeters, and average induration was 11–15 millimeters.

Smallpox Vaccine Local Reactions Among Susceptible Adults

- **Pain, swelling, erythema at vaccination site**
- **Regional lymphadenopathy**
  - –begins 3-10 days after vaccination
  - –can persist for 2-4 weeks after vaccination site heals

Some vaccinees may have larger degrees of erythema and induration that can be mistaken for cellulitis. These reactions generally improve within 24 to 48 hours without specific therapy but may require clinical evaluation to rule out bacterial cellulitis.

Forty to 47 percent of vaccinees reported mild pain at the site of inoculation. But 2%–3% reported the pain as severe. Axillary lymphadenopathy was reported in about one-third of recipients. Most lymphadenopathy was mild, but in 3%–7% it was considered moderate, i.e., bothersome to the vaccinee but not otherwise interfering with normal activities.

Fever is common after administration of smallpox vaccine. In a recent study of Dryvax given to unvaccinated adults, 5%–9% reported a temperature of 100°F (37.7°C) or higher, and 3% reported temperature of 102°F (38.8°C) or higher. Fever is most common 7–12 days after vaccination. In addition to fever, adult vaccinees also report a variety of constitutional symptoms, including headache, myalgias, chills, nausea, and fatigue on or about the eighth or ninth day after vaccination. One or 2 percent of recipients reported these symptoms as severe.

Smallpox Vaccine Reactions Among Susceptible Adults

- **Elevated temperature**
  - –5%–9% ≥100°F
  - –3% ≥102°F
- **Systemic symptoms (malaise, myalgia)**
- **36% sufficiently ill to miss work, school, or recreational activities or had trouble sleeping**

Historically, fever was more common among children. In past studies, about 70% of children experienced 1 or more days of temperature 100°F (37.7°C) or higher after primary vaccination. Fifteen to 20 percent of children experienced temperatures 102°F (38.8°C) or higher.

Smallpox Vaccine Adverse Reaction Rates*

Reaction	Primary Vaccination
Inadvertent inoculation	25-529
Generalized vaccinia	23-242
Eczema vaccinatum	10-39
Progressive vaccinia	0.9-1.5
Postvaccinial encephalitis	3-12
Death	1

*Rates per million primary vaccinations

Inadvertent Inoculation

- Caused by transfer of vaccinia virus from site of vaccination to other areas of the body
- Most commonly on face, eyelid, nose, mouth, rectum, genitalia
- Most lesions heal spontaneously without specific treatment

Generalized Vaccinia

- Results from viremia with implantations in the skin
- Occurs in the absence of eczema or other preexisting skin diseases
- Vesicles or pustules on normal skin distant from vaccination site
- Usually minor illness with little residual damage

Vaccinia virus is present at the site of vaccination beginning about 4 days after vaccination. Maximum viral shedding from the vaccination site occurs 4–14 days after vaccination, but vaccinia can be recovered from the site until the crust separates from the skin. **Inadvertent inoculation** (i.e., transfer of vaccinia from the vaccination site to another part of the body) is the most frequent complication of smallpox vaccination and accounts for approximately half of all complications of primary vaccination and revaccination. Studies in 1968 estimated the rate of inadvertent inoculation to be 529 cases per million primary vaccinations. The most common sites involved are the face, eyelid, nose, mouth, genitalia, and rectum. Most lesions heal without specific treatment. Involvement of the eye may result in scaring of the cornea and significant impairment of vision.

A variety of **erythematous or urticarial rashes** can occur approximately 10 days after primary vaccination. The vaccinee is usually afebrile with this reaction, and the rash resolves spontaneously within 2–4 days. In rare instances, bullous erythema multiforme (Stevens-Johnson syndrome) occurs.

Generalized vaccinia is another type of rash following smallpox vaccination. This condition is believed to result from a vaccinia viremia with implantations in the skin in persons without eczema or other preexisting skin disease. It consists of vesicles or pustules appearing on normal skin distant from the vaccination site. Most rashes labeled as generalized vaccinia produce only minor illness with little residual damage. The rash is generally self limited and requires minor or no therapy except among patients whose conditions might be toxic or who have serious underlying immunosuppressive illnesses. In the 1968 studies, rashes diagnosed as generalized vaccinia occurred at a rate of 242 per million primary vaccinations.

Moderate and severe complications of vaccinia vaccination include eczema vaccinatum, progressive vaccinia, and post-vaccinial encephalitis. These complications are rare but occur at least 10 times more often among primary vaccinees than among revaccinees and are more frequent among infants than among older children and adults. It is estimated that 14–52 persons per million primary vaccinations will experience potentially life-threatening adverse reactions.

Myopericarditis is the inflammation of heart muscle and/or the membrane that surrounds the heart. There were reports of this condition following smallpox vaccination in the 1950s and 1960s, but these cases were associated with vaccine strains not currently used. Myopericarditis was not an anticipated adverse reaction to the smallpox vaccine when the National Smallpox Vaccination Program began in

December 2002. During January–October 2003, 31 serious cardiac adverse events were reported among approximately 38,000 civilian recipients of smallpox vaccine (21 myopericarditis and 10 ischemic events).

Eczema vaccinatum is a localized or systemic dissemination of vaccinia virus in persons who have eczema or atopic dermatitis or a history of either of these conditions, or among contacts of vaccinees with eczema or atopic dermatitis or a history of these skin conditions. **Eczema vaccinatum can occur regardless of whether the skin disease is active or quiescent**. Usually the illness is mild and self limited, but it can be severe or fatal. The most serious cases among vaccine recipients occur among primary vaccinees. Severe cases have been observed after recently vaccinated persons have been in contact with persons who have active eczema or atopic dermatitis or a history of these skin conditions. In the 1968 studies, eczema vaccinatum was estimated to occur in 10–39 persons per million primary vaccinations.

Eczema Vaccinatum

- Generalized spread of vaccinia on skin of patients with eczema or atopic dermatitis, or past history of eczema or atopic dermatitis
- Occurs in vaccinees and contacts
- Can occur whether eczema is active or quiescent
- May be severe or fatal

Progressive vaccinia, also known as vaccinia necrosum, is a severe illness characterized by progressive necrosis in the area of vaccination, often with metastatic lesions. It occurs almost exclusively among persons with cellular immunodeficiency, but it can occur in persons with humoral immunodeficiency. In the 1968 studies, it occurred in approximately 1–2 persons per million primary vaccinations. Progressive vaccinia was almost always fatal before the introduction of vaccinia immune globulin and antiviral agents. Progressive vaccinia may be more common now, with human immunodeficiency virus (HIV) and post-transplant immunosuppression widely prevalent. Therapy includes aggressive treatment with vaccinia immune globulin and possibly antiviral drugs.

Progressive Vaccinia

- Progressive necrosis at site of vaccination, often with metastatic lesions
- Occurs in patients with impaired immunologic function, particularly cellular immunodeficiency
- Frequently fatal

Postvaccinial encephalitis has been reported in 3–12 persons per million primary vaccinations. In the majority of cases, postvaccinal encephalitis affects primary vaccinees younger than 12 months of age or adolescents and adults receiving a primary vaccination. It presents with any of a variety of central nervous system signs, such as ataxia, confusion, paralysis, seizures, or coma. Most cases are believed to result from autoimmune or allergic reactions rather than direct viral invasion of the nervous system. Approximately 15%–25% percent of affected vaccinees with this complication die, and 25% develop permanent neurologic sequelae. There is no specific therapy for postvaccinial encephalitis.

Postvaccinal Encephalitis

- Highest risk among children <12 months of age and older persons receiving primary vaccination
- Believed to result from autoimmune or allergic reaction
- Frequently fatal or neurologic sequelae

Fetal vaccinia is a rare complication of smallpox vaccination. Fewer than 50 cases of fetal vaccinia infection have been reported, usually after primary vaccination of the mother in early pregnancy. Fetal vaccinia usually results in stillbirth or death of the infant soon after delivery. Smallpox vaccine is not known to cause congenital malformations.

Fetal Vaccinia

- <50 fetal vaccinia cases reported in world literature
- Most result from primary vaccination of mother early in pregnancy
- Usually results in stillbirth or death of infant soon after delivery
- Congenital malformations not reported

Death resulting from smallpox vaccination is rare, with approximately one death per million primary vaccinations and one death per 4 million revaccinations. Death is most often the result of postvaccinial encephalitis or progressive vaccinia.

Guidelines for the evaluation and management of adverse reactions following smallpox vaccine were published in 2003 in the *Morbidity and Mortality Weekly Report* (*MMWR*). These guidelines are available on the CDC smallpox website at http://www.bt.cdc.gov/agent/smallpox/

Contraindications and Precautions to Vaccination

As with all vaccines, smallpox vaccine is contraindicated for persons who have experienced a severe allergic reaction to a prior dose of vaccine or to a vaccine component. Calf lymph vaccine (Dryvax) contains trace amounts of polymyxin B, streptomycin, tetracycline, and neomycin. The diluent contains glycerin and phenol. The vaccine does not contain sulfa-type antibiotics or penicillin. The new cell-culture vaccines do not contain antibiotics.

Smallpox Vaccine Contraindications and Precautions (Nonemergency Situations)

- Severe allergic reaction to a vaccine component or following a prior dose
- Immunosuppression in the recipient or household contact
- Physician-diagnosed heart disease or risk factors for heart disease
- Pregnancy in the recipient or household contact
- Breastfeeding

Persons with significant **immunosuppression** or those who have an **immunosuppressed household contact** should not receive smallpox vaccine in a nonemergency situation. Replication of vaccinia virus can be enhanced among people with immunodeficiency diseases and immunosuppression. Significant immunosuppression can be caused by many diseases, including leukemia, lymphoma, or generalized malignancy; solid organ or stem cell transplantation; and cellular or humoral immunity disorders, including HIV infection. Some autoimmune conditions and/or drugs used to treat autoimmune conditions may cause significant immunosuppression. Therapies that can cause immunosuppression include alkylating agents, antimetabolites, radiation, or high-dose corticosteroid therapy. Many experts suggest that prednisone doses of 2 milligrams per kilogram of body weight per day or higher, or 20 milligrams per day or higher for 14 days or more be considered immunosuppressive for the purpose of live virus vaccination. As with other live vaccines, those receiving high levels of these drugs should not be immunized for 3 months after their last dose.

Persons with physician-diagnosed **heart disease** should not receive the smallpox vaccine. This recommendation is based on findings of cardiac symptoms such as chest pain, palpitations and shortness of breath that were first detected in late March 2003, and is further supported by the recognition of myopericarditis as an adverse reaction. In addition to physician-diagnosed heart disease, persons with three of the

five heart disease **risk factors** (hypertension, hyperlipidemia, current smoker, diabetes or a first degree relative with a heart condition before the age of 50) are contraindicated from receiving the smallpox vaccine.

Live viral vaccines are contraindicated during **pregnancy**. For nonemergency indications, smallpox vaccine should not be administered to pregnant women or persons with a pregnant household contact. Pregnancy should also be avoided for at least 4 weeks after vaccination. Women who are breastfeeding should not be vaccinated because the close contact that occurs during this activity could increase the chance of transmission of the vaccine virus to the breastfeeding infant.

Because of the increased risk for eczema vaccinatum, smallpox vaccine should not be administered to persons with **eczema or atopic dermatitis or a past history of these conditions**. Persons who have a household contact with eczema or atopic dermatitis or a history of these conditions should also not be vaccinated.

Smallpox Vaccine Contraindications and Precautions (Nonemergency Situations)

- Eczema or atopic dermatitis (current or past history) in the recipient or household contact
- Acute, chronic, or exfoliative skin conditions (until improved or resolved) in the recipient or household contact
- Children <12 months of age
- Moderate or severe acute illness

Persons with other types of **acute, chronic, or exfoliative skin conditions** (e.g., burns, varicella, herpes zoster, impetigo, severe acne, or psoriasis) may be at increased risk of inadvertent inoculation. People with exfoliative skin conditions should not be vaccinated until the condition is controlled or resolves. In addition, persons with household contacts with acute, chronic, or exfoliative skin conditions should not be vaccinated until the skin condition in the household contact is controlled or resolves.

Children younger than 12 months of age should not be vaccinated. All vaccinated persons should take precautions to prevent virus transmission to young children and other household contacts. Since smallpox vaccine is currently recommended only for persons with occupational risk of exposure to vaccinia or recombinant vaccinia viruses, and for healthcare and public health response team members, vaccination is not indicated for infants or children younger than 18 years of age.

As with all vaccines, vaccination should be deferred for persons with **moderate or severe acute illnesses**.

In the event of an exposure to smallpox, there would be no contraindications to vaccination. In this situation, the benefit of vaccination would outweigh the risk of a complication from the vaccine. In a postrelease situation, contraindications and precautions for use of smallpox vaccine in a person who has not been exposed to smallpox would be the same as those in a nonemergency situation.

Smallpox Vaccine Contraindications and Precautions Emergency (Postrelease) Situations

- Exposed persons—no contraindications
- Unexposed persons—same as nonemergency situations

Vaccinia Immune Globulin Intravenous

- Immunoglobulin fraction of plasma from persons vaccinated with vaccinia vaccine
- Effective for treatment of eczema vaccinatum, progressive vaccinia, severe generalized vaccinia, and ocular vaccinia
- Not effective in postvaccinial encephalitis

Vaccinia Immune Globulin Intravenous

Vaccinia immune globulin intravenous (VIGIV) is the only product currently available for treatment of complications of vaccinia vaccination. VIGIV is a solvent/detergent-treated sterile solution of purified gamma globulin (IgG) fraction of human plasma containing antibodies to vaccinia virus. It is manufactured from plasma collected from healthy, screened donors with high titers of anti-vaccinia antibody. Each plasma donation used for the manufacture of VIGIV is tested for the presence of hepatitis B virus and antibodies to human immunodeficiency viruses 1 and 2 and hepatitis C virus.

VIGIV is indicated for treatment or modification of eczema vaccinatum, progressive vaccinia, and severe generalized vaccinia. It should also be used for vaccinia infections in persons who have skin conditions such as burns, impetigo, varicella zoster, or poison ivy; or for persons who have eczematous skin lesions when it is warranted because of either the activity or extensiveness of such lesions. It is also indicated for aberrant infections induced by vaccinia virus, which include its accidental implantation in eyes (except in cases of isolated keratitis), mouth, or other areas where vaccinia infection would constitute a special hazard. Since postvaccinial encephalitis is not due to virus multiplication, VIGIV is not likely to be effective in treating this adverse reaction. Immune globulin products have no role in the treatment of smallpox.

Supplies of VIGIV are stored in the Strategic National Stockpile. All releases of VIGIV from the stockpile must be approved by CDC.

Antiviral Drugs

Cidofovir is an antiviral medication that is currently licensed for the treatment of retinitis. In vitro and animal studies with this drug have shown some activity against vaccinia virus, but it is unclear how well it would work in treating vaccinia infections in humans. Because it is not licensed for this indication, use of cidofovir for treating vaccinia infections should be done through an investigational new drug (IND) protocol with careful monitoring. Cidofovir is a second-line treatment for complications of smallpox vaccination. VIGIV is still considered the standard treatment. CDC is developing the investigative protocol for use of this drug.

Vaccine Storage and Handling

- Stable indefinitely at -4°F (-20°C)
- Store unreconstituted vaccine at 35-46°F (2°-8°C)
- Reconstituted vaccine must be used within 90 days
- Avoid contamination after opening vial

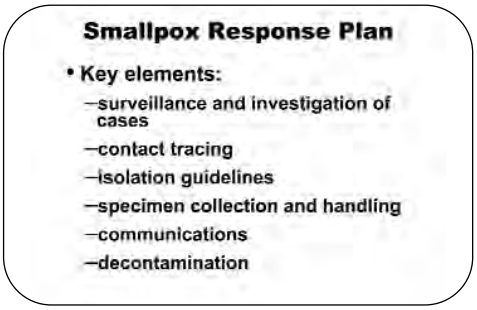
Vaccine Storage and Handling

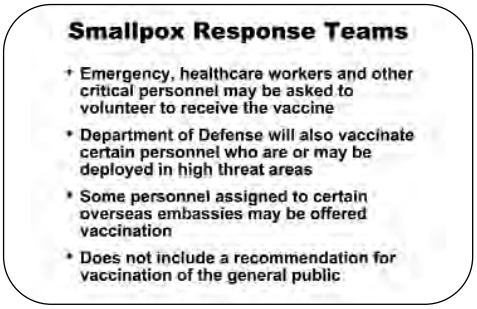
Lyophylized smallpox vaccine is stable indefinitely at temperatures of -4°F (-20°C) or less. Unreconstituted vaccine should be stored at refrigerator temperature 35°–40°F (2°–8°C). The vaccine should be used within 90 days of reconstitution. Because the vaccine vial must be opened in

order to prepare a dose for administration (i.e., the bifurcated needle is dipped into the vaccine), care must be taken to avoid contamination. A needle should never contact the vaccine in a vial more than once.

Smallpox Preparedness and Response Planning

A smallpox response plan has been in place in the United States since the early 1970s. In 1999, efforts were begun to update the response plan in the context of an intentional release of smallpox virus as an act of terrorism. Following the anthrax attacks in 2001, the plan was revised further to provide detailed information on surveillance and response to a smallpox virus release.





The interim plan is intended to assist with local and state response planning by identifying actions that must be taken in the event of a suspected smallpox case. **The key elements of preparedness for smallpox response are surveillance and diagnosis to achieve early detection of an introduced case; isolation of the case or cases; and identification and vaccination of the contacts of the case-patient or patients**. Sections of the plan provide detailed information on these critical aspects of the plan, including surveillance and contact tracing, smallpox vaccine, isolation guidelines for both confirmed and suspected cases and febrile contacts of patients, specimen collection and transport, decontamination, and communication.

In December 2002, the President announced a plan to better protect the American people against the threat of smallpox attack. The Department of Health and Human Services will work with state and local governments to form volunteer Smallpox Response Teams, which can provide critical services in the event of a smallpox attack. To ensure that Smallpox Response Teams can mobilize immediately in an emergency, healthcare workers and other critical personnel may be asked to volunteer to receive the vaccine. The Department of Defense will also vaccinate certain military and civilian personnel who are or may be deployed in high-threat areas. Some U.S. personnel assigned to certain overseas embassies may also be offered vaccination. The plan does not include a recommendation for vaccination of the general public.

Selected References

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APPENDIX A
Schedules and Recommendations

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Appendix A

Immunization Schedules on the Web

Childhood and Adolescent Immunization Schedule Schedule:

www.cdc.gov/vaccines/recs/schedules/child-schedule.htm

Contains:

- English and Spanish versions
- Color and black & white versions
- 4-page, 2-page, and pocket-size versions
- Palm OS and Pocket PC Handheld versions
- Screenreader accessible version
- Downloadable files for office printing or commercial printing
- Link to past years' schedules
- Interactive childhood vaccine scheduler
- more . . .

Adult Immunization Schedule Schedule:

www.cdc.gov/vaccines/recs/schedules/adult-schedule.htm

Contains:

- Color and black & white versions
- 4-page, 2-page, and pocket-size versions
- Downloadable files for office printing or commercial printing
- Screenreader accessible version
- Summary of changes since last year's version
- Adult vaccination screening form
- Adult and adolescent vaccine "quiz"
- more . . .

Appendix A

Recommended Immunization Schedule for Persons Aged 0 Through 6 Years—United States • 2009

For those who fall behind or start late, see the catch-up schedule

Vaccine ▼ Age ►	Birth	1 month	2 months	4 months	6 months	12 months	15 months	18 months	19–23 months	2–3 years	4–6 years
Hepatitis B[1]	HepB	HepB		see footnote 1	HepB						
Rotavirus[2]			RV	RV	RV[2]						
Diphtheria, Tetanus, Pertussis[3]			DTaP	DTaP	DTaP	see footnote 3	DTaP				DTaP
Haemophilus influenzae type b[4]			Hib	Hib	Hib[4]	Hib					
Pneumococcal[5]			PCV	PCV	PCV	PCV				PPSV	
Inactivated Poliovirus			IPV	IPV	IPV		IPV				IPV
Influenza[6]					Influenza (Yearly)						
Measles, Mumps, Rubella[7]						MMR		see footnote 7			MMR
Varicella[8]						Varicella		see footnote 8			Varicella
Hepatitis A[9]						HepA (2 doses)				HepA Series	
Meningococcal[10]										MCV	

Range of recommended ages

Certain high-risk groups

This schedule indicates the recommended ages for routine administration of currently licensed vaccines, as of December 1, 2008, for children aged 0 through 6 years. Any dose not administered at the recommended age should be administered at a subsequent visit, when indicated and feasible. Licensed combination vaccines may be used whenever any component of the combination is indicated and other components are not contraindicated and if approved by the Food and Drug Administration for that dose of the series. Providers should consult the relevant Advisory Committee on Immunization Practices statement for detailed recommendations, including high-risk conditions: http://www.cdc.gov/vaccines/pubs/acip-list.htm. Clinically significant adverse events that follow immunization should be reported to the Vaccine Adverse Event Reporting System (VAERS). Guidance about how to obtain and complete a VAERS form is available at http://www.vaers.hhs.gov or by telephone, 800-822-7967.

1. Hepatitis B vaccine (HepB). ***(Minimum age: birth)***

At birth:

- Administer monovalent HepB to all newborns before hospital discharge.
- If mother is hepatitis B surface antigen (HBsAg)-positive, administer HepB and 0.5 mL of hepatitis B immune globulin (HBIG) within 12 hours of birth.
- If mother's HBsAg status is unknown, administer HepB within 12 hours of birth. Determine mother's HBsAg status as soon as possible and, if HBsAg-positive, administer HBIG (no later than age 1 week).

After the birth dose:

- The HepB series should be completed with either monovalent HepB or a combination vaccine containing HepB. The second dose should be administered at age 1 or 2 months. The final dose should be administered no earlier than age 24 weeks.
- Infants born to HBsAg-positive mothers should be tested for HBsAg and antibody to HBsAg (anti-HBs) after completion of at least 3 doses of the HepB series, at age 9 through 18 months (generally at the next well-child visit).

4-month dose:

- Administration of 4 doses of HepB to infants is permissible when combination vaccines containing HepB are administered after the birth dose.

2. Rotavirus vaccine (RV). ***(Minimum age: 6 weeks)***

- Administer the first dose at age 6 through 14 weeks (maximum age: 14 weeks 6 days). Vaccination should not be initiated for infants aged 15 weeks or older (i.e., 15 weeks 0 days or older).
- Administer the final dose in the series by age 8 months 0 days.
- If Rotarix® is administered at ages 2 and 4 months, a dose at 6 months is not indicated.

3. Diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP). ***(Minimum age: 6 weeks)***

- The fourth dose may be administered as early as age 12 months, provided at least 6 months have elapsed since the third dose.
- Administer the final dose in the series at age 4 through 6 years.

4. *Haemophilus influenzae* type b conjugate vaccine (Hib). ***(Minimum age: 6 weeks)***

- If PRP-OMP (PedvaxHIB® or Comvax® [HepB-Hib]) is administered at ages 2 and 4 months, a dose at age 6 months is not indicated.
- TriHiBit® (DTaP/Hib) should not be used for doses at ages 2, 4, or 6 months but can be used as the final dose in children aged 12 months or older.

5. Pneumococcal vaccine. ***(Minimum age: 6 weeks for pneumococcal conjugate vaccine [PCV]; 2 years for pneumococcal polysaccharide vaccine [PPSV])***

- PCV is recommended for all children aged younger than 5 years. Administer 1 dose of PCV to all healthy children aged 24 through 59 months who are not completely vaccinated for their age.
- Administer PPSV to children aged 2 years or older with certain underlying medical conditions (see *MMWR* 2000;49[No. RR-9]), including a cochlear implant.

6. Influenza vaccine. ***(Minimum age: 6 months for trivalent inactivated influenza vaccine [TIV]; 2 years for five, attenuated influenza vaccine [LAIV])***

- Administer annually to children aged 6 months through 18 years.
- For healthy nonpregnant persons (i.e., those who do not have underlying medical conditions that predispose them to influenza complications) aged 2 through 49 years, either LAIV or TIV may be used.
- Children receiving TIV should receive 0.25 mL if aged 6 through 35 months or 0.5 mL if aged 3 years or older.
- Administer 2 doses (separated by at least 4 weeks) to children aged younger than 9 years who are receiving influenza vaccine for the first time or who were vaccinated for the first time during the previous influenza season but only received 1 dose.

7. Measles, mumps, and rubella vaccine (MMR). ***(Minimum age: 12 months)***

- Administer the second dose at age 4 through 6 years. However, the second dose may be administered before age 4, provided at least 28 days have elapsed since the first dose.

8. Varicella vaccine. ***(Minimum age: 12 months)***

- Administer the second dose at age 4 through 6 years. However, the second dose may be administered before age 4, provided at least 3 months have elapsed since the first dose.
- For children aged 12 months through 12 years the minimum interval between doses is 3 months. However, if the second dose was administered at least 28 days after the first dose, it can be accepted as valid.

9. Hepatitis A vaccine (HepA). ***(Minimum age: 12 months)***

- Administer to all children aged 1 year (i.e., aged 12 through 23 months). Administer 2 doses at least 6 months apart.
- Children not fully vaccinated by age 2 years can be vaccinated at subsequent visits.
- HepA also is recommended for children older than 1 year who live in areas where vaccination programs target older children or who are at increased risk of infection. See *MMWR* 2006;55(No. RR-7).

10. Meningococcal vaccine. ***(Minimum age: 2 years for meningococcal conjugate vaccine [MCV] and for meningococcal polysaccharide vaccine [MPSV])***

- Administer MCV to children aged 2 through 10 years with terminal complement component deficiency, anatomic or functional asplenia, and certain other high-risk groups. See *MMWR* 2005;54(No. RR-7).
- Persons who received MPSV 3 or more years previously and who remain at increased risk for meningococcal disease should be revaccinated with MCV.

The Recommended Immunization Schedules for Persons Aged 0 Through 18 Years are approved by the Advisory Committee on Immunization Practices (www.cdc.gov/vaccines/recs/acip), the American Academy of Pediatrics (http://www.aap.org), and the American Academy of Family Physicians (http://www.aafp.org).

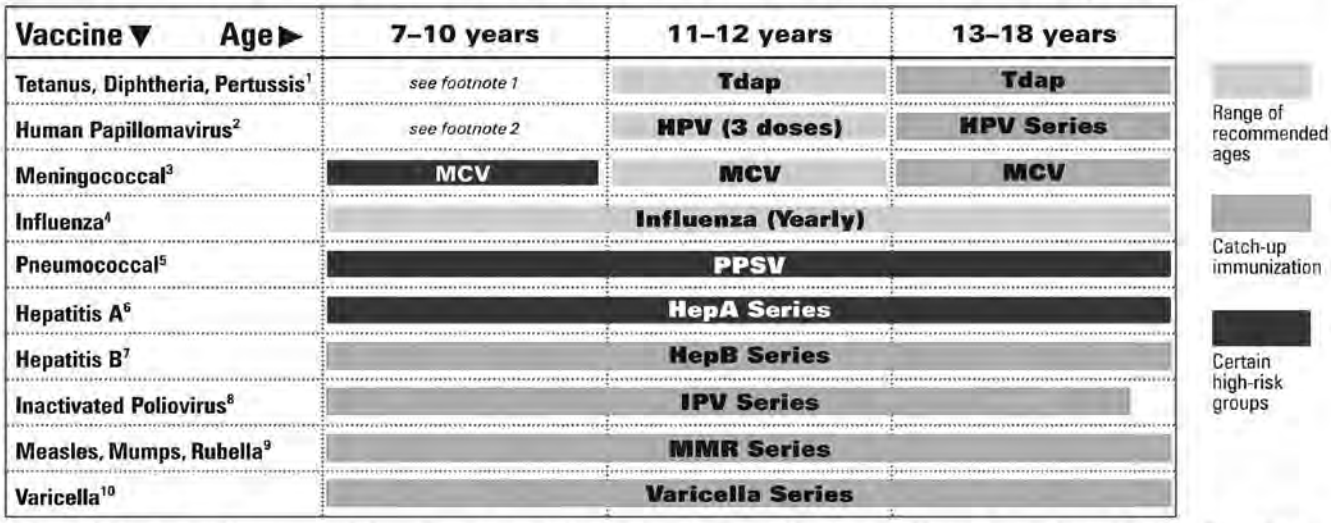
DEPARTMENT OF HEALTH AND HUMAN SERVICES • CENTERS FOR DISEASE CONTROL AND PREVENTION

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A

Recommended Immunization Schedule for Persons Aged 7 Through 18 Years—United States • 2009

For those who fall behind or start late, see the schedule below and the catch-up schedule



This schedule indicates the recommended ages for routine administration of currently licensed vaccines, as of December 1, 2008, for children aged 7 through 18 years. Any dose not administered at the recommended age should be administered at a subsequent visit, when indicated and feasible. Licensed combination vaccines may be used whenever any component of the combination is indicated and other components are not contraindicated and if approved by the Food and Drug Administration for that dose of the series. Providers should consult the relevant Advisory Committee on Immunization Practices statement for detailed recommendations, including high-risk conditions: http://www.cdc.gov/vaccines/pubs/acip-list.htm. Clinically significant adverse events that follow immunization should be reported to the Vaccine Adverse Event Reporting System (VAERS). Guidance about how to obtain and complete a VAERS form is available at http://www.vaers.hhs.gov or by telephone, 800-822-7967.

1. Tetanus and diphtheria toxoids and acellular pertussis vaccine (Tdap). ***(Minimum age: 10 years for BOOSTRIX® and 11 years for ADACEL®)***
- Administer at age 11 or 12 years for those who have completed the recommended childhood DTP/DTaP vaccination series and have not received a tetanus and diphtheria toxoid (Td) booster dose.
- Persons aged 13 through 18 years who have not received Tdap should receive a dose.
- A 5-year interval from the last Td dose is encouraged when Tdap is used as a booster dose; however, a shorter interval may be used if pertussis immunity is needed.

2. Human papillomavirus vaccine (HPV). ***(Minimum age: 9 years)***
- Administer the first dose to females at age 11 or 12 years.
- Administer the second dose 2 months after the first dose and the third dose 6 months after the first dose (at least 24 weeks after the first dose).
- Administer the series to females at age 13 through 18 years if not previously vaccinated.

3. Meningococcal conjugate vaccine (MCV).
- Administer at age 11 or 12 years, or at age 13 through 18 years if not previously vaccinated.
- Administer to previously unvaccinated college freshmen living in a dormitory.
- MCV is recommended for children aged 2 through 10 years with terminal complement component deficiency, anatomic or functional asplenia, and certain other groups at high risk. See *MMWR* 2005;54(No. RR-7).
- Persons who received MPSV 5 or more years previously and remain at increased risk for meningococcal disease should be revaccinated with MCV.

4. Influenza vaccine.
- Administer annually to children aged 6 months through 18 years.
- For healthy nonpregnant persons (i.e., those who do not have underlying medical conditions that predispose them to influenza complications) aged 2 through 49 years, either LAIV or TIV may be used.
- Administer 2 doses (separated by at least 4 weeks) to children aged younger than 9 years who are receiving influenza vaccine for the first time or who were vaccinated for the first time during the previous influenza season but only received 1 dose.

5. Pneumococcal polysaccharide vaccine (PPSV).
- Administer to children with certain underlying medical conditions (see *MMWR* 1997;46[No. RR-8]), including a cochlear implant. A single revaccination should be administered to children with functional or anatomic asplenia or other immunocompromising condition after 5 years.

6. Hepatitis A vaccine (HepA).
- Administer 2 doses at least 6 months apart.
- HepA is recommended for children older than 1 year who live in areas where vaccination programs target older children or who are at increased risk of infection. See *MMWR* 2006;55(No. RR-7).

7. Hepatitis B vaccine (HepB).
- Administer the 3-dose series to those not previously vaccinated.
- A 2-dose series (separated by at least 4 months) of adult formulation Recombivax HB® is licensed for children aged 11 through 15 years.

8. Inactivated poliovirus vaccine (IPV).
- For children who received an all-IPV or all-oral poliovirus (OPV) series, a fourth dose is not necessary if the third dose was administered at age 4 years or older.
- If both OPV and IPV were administered as part of a series, a total of 4 doses should be administered, regardless of the child's current age.

9. Measles, mumps, and rubella vaccine (MMR).
- If not previously vaccinated, administer 2 doses or the second dose for those who have received only 1 dose, with at least 28 days between doses.

10. Varicella vaccine.
- For persons aged 7 through 18 years without evidence of immunity (see *MMWR* 2007;56[No. RR-4]), administer 2 doses if not previously vaccinated or the second dose if they have received only 1 dose.
- For persons aged 7 through 12 years, the minimum interval between doses is 3 months. However, if the second dose was administered at least 28 days after the first dose, it can be accepted as valid.
- For persons aged 13 years and older, the minimum interval between doses is 28 days.

The Recommended Immunization Schedules for Persons Aged 0 Through 18 Years are approved by the Advisory Committee on Immunization Practices (www.cdc.gov/vaccines/recs/acip), the American Academy of Pediatrics (http://www.aap.org), and the American Academy of Family Physicians (http://www.aafp.org).

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Appendix A

Catch-up Immunization Schedule for Persons Aged 4 Months Through 18 Years Who Start Late or Who Are More Than 1 Month Behind—United States • 2009

The table below provides catch-up schedules and minimum intervals between doses for children whose vaccinations have been delayed. A vaccine series does not need to be restarted, regardless of the time that has elapsed between doses. Use the section appropriate for the child's age.

Vaccine	Minimum Age for Dose 1	Minimum Interval Between Doses			
		Dose 1 to Dose 2	Dose 2 to Dose 3	Dose 3 to Dose 4	Dose 4 to Dose 5
CATCH-UP SCHEDULE FOR PERSONS AGED 4 MONTHS THROUGH 6 YEARS					
Hepatitis B[1]	Birth	4 weeks	8 weeks (and at least 16 weeks after first dose)		
Rotavirus[2]	6 wks	4 weeks	4 weeks[2]		
Diphtheria, Tetanus, Pertussis[3]	6 wks	4 weeks	4 weeks	6 months	6 months[3]
Haemophilus influenzae type b[4]	6 wks	4 weeks if first dose administered at younger than age 12 months 8 weeks (as final dose) if first dose administered at age 12-14 months No further doses needed if first dose administered at age 15 months or older	4 weeks[4] if current age is younger than 12 months 8 weeks (as final dose)[4] if current age is 12 months or older and second dose administered at younger than age 15 months No further doses needed if previous dose administered at age 15 months or older	8 weeks (as final dose) This dose only necessary for children aged 12 months through 59 months who received 3 doses before age 12 months	
Pneumococcal[5]	6 wks	4 weeks if first dose administered at younger than age 12 months 8 weeks (as final dose for healthy children) if first dose administered at age 12 months or older or current age 24 through 59 months No further doses needed for healthy children if first dose administered at age 24 months or older	4 weeks if current age is younger than 12 months 8 weeks (as final dose for healthy children) if current age is 12 months or older No further doses needed for healthy children if previous dose administered at age 24 months or older	8 weeks (as final dose) This dose only necessary for children aged 12 months through 59 months who received 3 doses before age 12 months or for high-risk children who received 3 doses at any age	
Inactivated Poliovirus[6]	6 wks	4 weeks	4 weeks	4 weeks[6]	
Measles, Mumps, Rubella[7]	12 mos	4 weeks			
Varicella[8]	12 mos	3 months			
Hepatitis A[9]	12 mos	6 months			
CATCH-UP SCHEDULE FOR PERSONS AGED 7 THROUGH 18 YEARS					
Tetanus, Diphtheria/ Tetanus, Diphtheria, Pertussis[10]	7 yrs[10]	4 weeks	4 weeks if first dose administered at younger than age 12 months 6 months if first dose administered at age 12 months or older	6 months if first dose administered at younger than age 12 months	
Human Papillomavirus[11]	9 yrs	Routine dosing intervals are recommended[11]			
Hepatitis A[9]	12 mos	6 months			
Hepatitis B[1]	Birth	4 weeks	8 weeks (and at least 16 weeks after first dose)		
Inactivated Poliovirus[6]	6 wks	4 weeks	4 weeks	4 weeks[6]	
Measles, Mumps, Rubella[7]	12 mos	4 weeks			
Varicella[8]	12 mos	3 months if the person is younger than age 13 years 4 weeks if the person is aged 13 years or older			

1. Hepatitis B vaccine (HepB).
- Administer the 3-dose series to those not previously vaccinated.
- A 2-dose series (separated by at least 4 months) of adult formulation Recombivax HB® is licensed for children aged 11 through 15 years.

2. Rotavirus vaccine (RV).
- The maximum age for the first dose is 14 weeks 6 days. Vaccination should not be initiated for infants aged 15 weeks or older (i.e., 15 weeks 0 days or older).
- Administer the final dose in the series by age 8 months 0 days.
- If Rotarix® was administered for the first and second doses, a third dose is not indicated.

3. Diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP).
- The fifth dose is not necessary if the fourth dose was administered at age 4 years or older.

4. *Haemophilus influenzae* type b conjugate vaccine (Hib).
- Hib vaccine is not generally recommended for persons aged 5 years or older. No efficacy data are available on which to base a recommendation concerning use of Hib vaccine for older children and adults. However, studies suggest good immunogenicity in persons who have sickle cell disease, leukemia, or HIV infection, or who have had a splenectomy; administering 1 dose of Hib vaccine to these persons is not contraindicated.
- If the first 2 doses were PRP-OMP (PedvaxHIB® or Comvax®), and administered at age 11 months or younger, the third (and final) dose should be administered at age 12 through 15 months and at least 8 weeks after the second dose.
- If the first dose was administered at age 7 through 11 months, administer 2 doses separated by 4 weeks and a final dose at age 12 through 15 months.

5. Pneumococcal vaccine.
- Administer 1 dose of pneumococcal conjugate vaccine (PCV) to all healthy children aged 24 through 59 months who have not received at least 1 dose of PCV on or after age 12 months.
- For children aged 24 through 59 months with underlying medical conditions, administer 1 dose of PCV if 3 doses were received previously or administer 2 doses of PCV at least 8 weeks apart if fewer than 3 doses were received previously.
- Administer pneumococcal polysaccharide vaccine (PPSV) to children aged 2 years or older with certain underlying medical conditions (see *MMWR* 2000;49[No. RR-9]), including a cochlear implant, at least 8 weeks after the last dose of PCV.

6. Inactivated poliovirus vaccine (IPV).
- For children who received an all-IPV or all-oral poliovirus (OPV) series, a fourth dose is not necessary if the third dose was administered at age 4 years or older.
- If both OPV and IPV were administered as part of a series, a total of 4 doses should be administered, regardless of the child's current age.

7. Measles, mumps, and rubella vaccine (MMR).
- Administer the second dose at age 4 through 6 years. However, the second dose may be administered before age 4, provided at least 28 days have elapsed since the first dose.
- If not previously vaccinated, administer 2 doses with at least 28 days between doses.

8. Varicella vaccine.
- Administer the second dose at age 4 through 6 years. However, the second dose may be administered before age 4, provided at least 3 months have elapsed since the first dose.
- For persons aged 12 months through 12 years, the minimum interval between doses is 3 months. However, if the second dose was administered at least 28 days after the first dose, it can be accepted as valid.
- For persons aged 13 years and older, the minimum interval between doses is 28 days.

9. Hepatitis A vaccine (HepA).
- HepA is recommended for children older than 1 year who live in areas where vaccination programs target older children or who are at increased risk of infection. See *MMWR* 2006;55(No. RR-7).

10. Tetanus and diphtheria toxoids vaccine (Td) and tetanus and diphtheria toxoids and acellular pertussis vaccine (Tdap).
- Doses of DTaP are counted as part of the Td/Tdap series.
- Tdap should be substituted for a single dose of Td in the catch-up series or as a booster for children aged 10 through 18 years; use Td for other doses.

11. Human papillomavirus vaccine (HPV).
- Administer the series to females at age 13 through 18 years if not previously vaccinated.
- Use recommended routine dosing intervals for series catch-up (i.e., the second and third doses should be administered at 2 and 6 months after the first dose). However, the minimum interval between the first and second doses is 4 weeks. The minimum interval between the second and third doses is 12 weeks, and the third dose should be given at least 24 weeks after the first dose.

Information about reporting reactions after immunization is available online at http://www.vaers.hhs.gov or by telephone, 800-822-7967. Suspected cases of vaccine-preventable diseases should be reported to the state or local health department. Additional information, including precautions and contraindications for immunization, is available from the National Center for Immunization and Respiratory Diseases at http://www.cdc.gov/vaccines or telephone, 800-CDC-INFO (800-232-4636).

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CS11388-A

A

Recommended Adult Immunization Schedule
UNITED STATES · 2009

Note: These recommendations *must* be read with the footnotes that follow containing number of doses, intervals between doses, and other important information.

Figure 1. Recommended adult immunization schedule, by vaccine and age group

VACCINE ▼ / AGE GROUP ▶	19–26 years	27–49 years	50–59 years	60–64 years	≥65 years
Tetanus, diphtheria, pertussis (Td/Tdap)[1,*]	Substitute 1-time dose of Tdap for Td booster; then boost with Td every 10 yrs				Td booster every 10 yrs
Human papillomavirus (HPV)[2,*]	3 doses (females)				
Varicella[3,*]	2 doses				
Zoster[4]				1 dose	
Measles, mumps, rubella (MMR)[5,*]	1 or 2 doses		1 dose		
Influenza[6,*]	1 dose annually				
Pneumococcal (polysaccharide)[7,8]	1 or 2 doses				1 dose
Hepatitis A[9,*]	2 doses				
Hepatitis B[10,*]	3 doses				
Meningococcal[11,*]	1 or more doses				

*Covered by the Vaccine Injury Compensation Program.

For all persons in this category who meet the age requirements and who lack evidence of immunity (e.g., lack documentation of vaccination or have no evidence of prior infection)

Recommended if some other risk factor is present (e.g., on the basis of medical, occupational, lifestyle, or other indications)

No recommendation

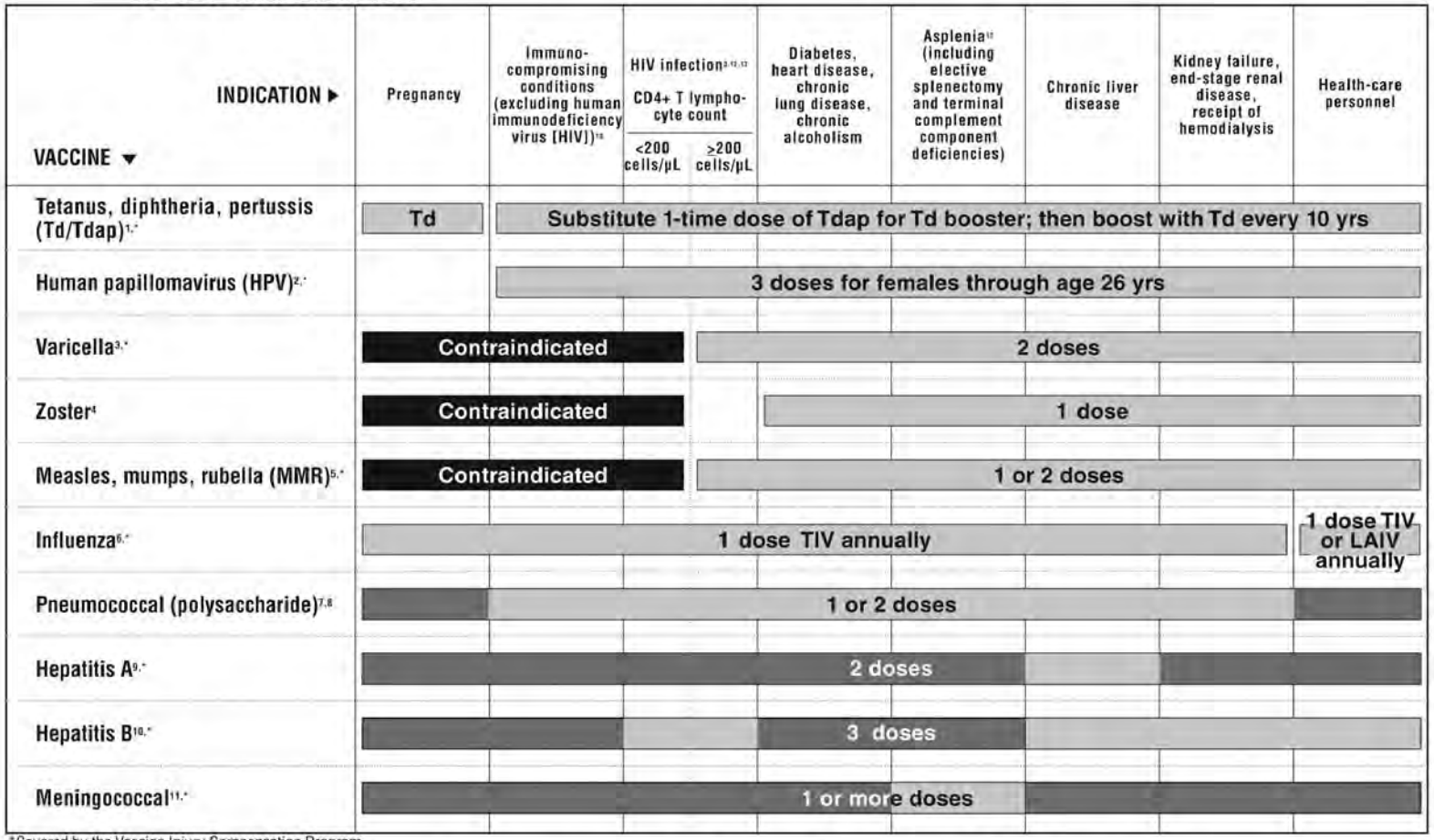
Report all clinically significant postvaccination reactions to the Vaccine Adverse Event Reporting System (VAERS). Reporting forms and instructions on filing a VAERS report are available at www.vaers.hhs.gov or by telephone, 800-822-7967.

Information on how to file a Vaccine Injury Compensation Program claim is available at www.hrsa.gov/vaccinecompensation or by telephone, 800-338-2382. To file a claim for vaccine injury, contact the U.S. Court of Federal Claims, 717 Madison Place, N.W., Washington, D.C. 20005; telephone, 202-357-6400.

Additional information about the vaccines in this schedule, extent of available data, and contraindications for vaccination is also available at www.cdc.gov/vaccines or from the CDC-INFO Contact Center at 800-CDC-INFO (800-232-4636) in English and Spanish, 24 hours a day, 7 days a week.

Use of trade names and commercial sources is for identification only and does not imply endorsement by the U.S. Department of Health and Human Services.

Figure 2. Vaccines that might be indicated for adults based on medical and other indications



*Covered by the Vaccine Injury Compensation Program.

For all persons in this category who meet the age requirements and who lack evidence of immunity (e.g., lack documentation of vaccination or have no evidence of prior infection)

Recommended if some other risk factor is present (e.g., on the basis of medical, occupational, lifestyle, or other indications)

No recommendation

These schedules indicate the recommended age groups and medical indications for which administration of currently licensed vaccines is commonly indicated for adults ages 19 years and older, as of January 1, 2009. Licensed combination vaccines may be used whenever any components of the combination are indicated and when the vaccine's other components are not contraindicated. For detailed recommendations on all vaccines, including those used primarily for travelers or that are issued during the year, consult the manufacturers' package inserts and the complete statements from the Advisory Committee on Immunization Practices (www.cdc.gov/vaccines/pubs/acip-list.htm).

C5200484-A

The recommendations in this schedule were approved by the Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP), the American Academy of Family Physicians (AAFP), the American College of Obstetricians and Gynecologists (ACOG), and the American College of Physicians (ACP).

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Footnotes

Recommended Adult Immunization Schedule—UNITED STATES - 2009

For complete statements by the Advisory Committee on Immunization Practices (ACIP), visit www.cdc.gov/vaccines/pubs/ACIP-list.htm.

1. Tetanus, diphtheria, and acellular pertussis (Td/Tdap) vaccination

Tdap should replace a single dose of Td for adults aged 19 through 64 years who have not received a dose of Tdap previously.

Adults with uncertain or incomplete history of primary vaccination series with tetanus and diphtheria toxoid-containing vaccines should begin or complete a primary vaccination series. A primary series for adults is 3 doses of tetanus and diphtheria toxoid-containing vaccines; administer the first 2 doses at least 4 weeks apart and the third dose 6–12 months after the second. However, Tdap can substitute for any one of the doses of Td in the 3-dose primary series. The booster dose of tetanus and diphtheria toxoid-containing vaccine should be administered to adults who have completed a primary series and if the last vaccination was received 10 or more years previously. Tdap or Td vaccine may be used, as indicated.

If a woman is pregnant and received the last Td vaccination 10 or more years previously, administer Td during the second or third trimester. If the woman received the last Td vaccination less than 10 years previously, administer Tdap during the immediate postpartum period. A dose of Tdap is recommended for postpartum women, close contacts of infants aged less than 12 months, and all health-care personnel with direct patient contact if they have not previously received Tdap. An interval as short as 2 years from the last Td is suggested; shorter intervals can be used. Td may be deferred during pregnancy and Tdap substituted in the immediate postpartum period, or Tdap may be administered instead of Td to a pregnant woman after an informed discussion with the woman.

Consult the ACIP statement for recommendations for administering Td as prophylaxis in wound management.

2. Human papillomavirus (HPV) vaccination

HPV vaccination is recommended for all females aged 11 through 26 years (and may begin at 9 years) who have not completed the vaccine series. History of genital warts, abnormal Papanicolaou test, or positive HPV DNA test is not evidence of prior infection with all vaccine HPV types. HPV vaccination is recommended for persons with such histories.

Ideally, vaccine should be administered before potential exposure to HPV through sexual activity; however, females who are sexually active should still be vaccinated consistent with age-based recommendations. Sexually active females who have not been infected with any of the four HPV vaccine types receive the full benefit of the vaccination. Vaccination is less beneficial for females who have already been infected with one or more of the HPV vaccine types.

A complete series consists of 3 doses. The second dose should be administered 2 months after the first dose; the third dose should be administered 6 months after the first dose.

HPV vaccination is not specifically recommended for females with the medical indications described in Figure 2, "Vaccines that might be indicated for adults based on medical and other indications." Because HPV vaccine is not a live-virus vaccine, it may be administered to persons with the medical indications described in Figure 2. However, the immune response and vaccine efficacy might be less for persons with the medical indications described in Figure 2 than in persons who do not have the medical indications described or who are immunocompetent. Health-care personnel are not at increased risk because of occupational exposure, and should be vaccinated consistent with age-based recommendations.

3. Varicella vaccination

All adults without evidence of immunity to varicella should receive 2 doses of single-antigen varicella vaccine if not previously vaccinated or the second dose if they have received only one dose unless they have a medical contraindication. Special consideration should be given to those who 1) have close contact with persons at high risk for severe disease (e.g., health-care personnel and family contacts of persons with immunocompromising conditions) or 2) are at high risk for exposure or transmission (e.g., teachers; child care employees; residents and staff members of institutional settings, including correctional institutions; college students; military personnel; adolescents and adults living in households with children; nonpregnant women of childbearing age; and international travelers).

Evidence of immunity to varicella in adults includes any of the following: 1) documentation of 2 doses of varicella vaccine at least 4 weeks apart; 2) U.S.-born before 1980 (although for health-care personnel and pregnant women, birth before 1980 should not be considered evidence of immunity); 3) history of varicella based on diagnosis or verification of varicella by a health-care provider (for a patient reporting a history of or presenting with an atypical case, a mild case, or both, health-care providers should seek either an epidemiologic link with a typical varicella case or to a laboratory-confirmed case or evidence of laboratory confirmation, if it was performed at the time of acute disease); 4) history of herpes zoster based on health-care provider diagnosis or verification of herpes zoster by a health-care provider; or 5) laboratory evidence of immunity or laboratory confirmation of disease.

Pregnant women should be assessed for evidence of varicella immunity. Women who do not have evidence of immunity should receive the first dose of varicella vaccine upon completion or termination of pregnancy and before discharge from the health-care facility. The second dose should be administered 4–8 weeks after the first dose.

4. Herpes zoster vaccination

A single dose of zoster vaccine is recommended for adults aged 60 years and older regardless of whether they report a prior episode of herpes zoster. Persons with chronic medical conditions may be vaccinated unless their condition constitutes a contraindication.

5. Measles, mumps, rubella (MMR) vaccination

Measles component: Adults born before 1957 generally are considered immune to measles. Adults born during or after 1957 should receive 1 or more doses of MMR unless they have a medical contraindication, documentation of 1 or more doses, history of measles based on health-care provider diagnosis, or laboratory evidence of immunity.

A second dose of MMR is recommended for adults who 1) have been recently exposed to measles or are in an outbreak setting; 2) have been vaccinated previously with killed measles vaccine; 3) have been vaccinated with an unknown type of measles vaccine during 1963–1967; 4) are students in postsecondary educational institutions; 5) work in a health-care facility; or 6) plan to travel internationally.

Mumps component: Adults born before 1957 generally are considered immune to mumps. Adults born during or after 1957 should receive 1 dose of MMR unless they have a medical contraindication, history of mumps based on health-care provider diagnosis, or laboratory evidence of immunity.

A second dose of MMR is recommended for adults who 1) live in a community experiencing a mumps outbreak and are in an affected age group; 2) are students in postsecondary educational institutions; 3) work in a health-care facility; or 4) plan to travel internationally. For unvaccinated health-care personnel born before 1957 who do not have other evidence of mumps immunity, administering 1 dose on a routine basis should be considered and administering a second dose during an outbreak should be strongly considered.

Rubella component: 1 dose of MMR vaccine is recommended for women whose rubella vaccination history is unreliable or who lack laboratory evidence of immunity. For women of childbearing age, regardless of birth year, rubella immunity should be determined and women should be counseled regarding congenital rubella syndrome. Women who do not have evidence of immunity should receive MMR upon completion or termination of pregnancy and before discharge from the health-care facility.

6. Influenza vaccination

Medical indications: Chronic disorders of the cardiovascular or pulmonary systems, including asthma; chronic metabolic diseases, including diabetes mellitus, renal or hepatic dysfunction, hemoglobinopathies, or immunocompromising conditions (including immunocompromising conditions caused by medications or human immunodeficiency virus [HIV]); any condition that compromises respiratory function or the handling of respiratory secretions or that can increase the risk of aspiration (e.g., cognitive dysfunction, spinal cord injury, or seizure disorder or other neuromuscular disorder); and pregnancy during the influenza season. No data exist on the risk for severe or complicated influenza disease among persons with asplenia; however, influenza is a risk factor for secondary bacterial infections that can cause severe disease among persons with asplenia.

Occupational indications: All health-care personnel, including those employed by long-term care and assisted-living facilities, and caregivers of children less than 5 years old.

Other indications: Residents of nursing homes and other long-term care and assisted-living facilities; persons likely to transmit influenza to persons at high risk (e.g., in-home household contacts and caregivers of children aged less than 5 years old, persons 65 years old and older and persons of all ages with high-risk condition[s]); and anyone who would like to decrease their risk of getting influenza. Healthy, nonpregnant adults aged less than 50 years without high-risk medical conditions who are not contacts of severely immunocompromised persons in special care units can receive either intranasally administered live, attenuated influenza vaccine (FluMist®) or inactivated vaccine. Other persons should receive the inactivated vaccine.

7. Pneumococcal polysaccharide (PPSV) vaccination

Medical indications: Chronic lung disease (including asthma); chronic cardiovascular diseases; diabetes mellitus; chronic liver diseases, cirrhosis; chronic alcoholism, chronic renal failure or nephrotic syndrome; functional or anatomic asplenia (e.g., sickle cell disease or splenectomy [if elective splenectomy is planned, vaccinate at least 2 weeks before surgery]); immunocompromising conditions; and cochlear implants and cerebrospinal fluid leaks. Vaccinate as close to HIV diagnosis as possible.

Other indications: Residents of nursing homes or long-term care facilities and persons who smoke cigarettes. Routine use of PPSV is not recommended for Alaska Native or American Indian persons younger than 65 years unless they have underlying medical conditions that are PPSV indications. However public health authorities may consider recommending PPSV for Alaska Natives and American Indians aged 50 through 64 years who are living in areas in which the risk of invasive pneumococcal disease is increased.

8. Revaccination with PPSV

One-time revaccination after 5 years for persons with chronic renal failure or nephrotic syndrome; functional or anatomic asplenia (e.g., sickle cell disease or splenectomy); and for persons with immunocompromising conditions. For persons aged 65 years and older, one-time revaccination if they were vaccinated 5 or more years previously and were aged less than 65 years at the time of primary vaccination.

9. Hepatitis A vaccination

Medical indications: Persons with chronic liver disease and persons who receive clotting factor concentrates.

Behavioral indications: Men who have sex with men and persons who use illegal drugs.

Occupational indications: Persons working with hepatitis A virus (HAV)-infected primates or with HAV in a research laboratory setting.

Other indications: Persons traveling to or working in countries that have high or intermediate endemicity of hepatitis A (a list of countries is available at www.cdc.gov/travel/contentdiseases.aspx) and any person seeking protection from HAV infection.

Single-antigen vaccine formulations should be administered in a 2-dose schedule at either 0 and 6–12 months (Havrix®), or 0 and 6–18 months (Vaqta®). If the combined hepatitis A and hepatitis B vaccine (Twinrix®) is used, administer 3 doses at 0, 1, and 6 months; alternatively, a 4-dose schedule, administered on days 0, 7 and 21 to 30 followed by a booster dose at month 12 may be used.

10. Hepatitis B vaccination

Medical indications: Persons with end-stage renal disease, including patients receiving hemodialysis; persons with HIV infection; and persons with chronic liver disease.

Occupational indications: Health-care personnel and public-safety workers who are exposed to blood or other potentially infectious body fluids.

Behavioral indications: Sexually active persons who are not in a long-term, mutually monogamous relationship (e.g., persons with more than 1 sex partner during the previous 6 months); persons seeking evaluation or treatment for a sexually transmitted disease; current or recent injection-drug users; and men who have sex with men.

Other indications: Household contacts and sex partners of persons with chronic hepatitis B virus (HBV) infection; clients and staff members of institutions for persons with developmental disabilities; international travelers to countries with high or intermediate prevalence of chronic HBV infection (a list of countries is available at www.cdc.gov/travel/contentdiseases.aspx); and any adult seeking protection from HBV infection.

Hepatitis B vaccination is recommended for all adults in the following settings: STD treatment facilities; HIV testing and treatment facilities; facilities providing drug-abuse treatment and prevention services; health-care settings targeting services to injection-drug users or men who have sex with men; correctional facilities; end-stage renal disease programs and facilities for chronic hemodialysis patients; and institutions and nonresidential daycare facilities for persons with developmental disabilities.

If the combined hepatitis A and hepatitis B vaccine (Twinrix®) is used, administer 3 doses at 0, 1, and 6 months; alternatively, a 4-dose schedule, administered on days 0, 7 and 21 to 30 followed by a booster dose at month 12 may be used.

Special formulation indications: For adult patients receiving hemodialysis or with other immunocompromising conditions, 1 dose of 40 µg/mL (Recombivax HB®) administered on a 3-dose schedule or 2 doses of 20 µg/mL (Engerix-B®) administered simultaneously on a 4-dose schedule at 0, 1, 2 and 6 months.

11. Meningococcal vaccination

Medical indications: Adults with anatomic or functional asplenia, or terminal complement component deficiencies.

Other indications: First-year college students living in dormitories; microbiologists who are routinely exposed to isolates of *Neisseria meningitidis*; military recruits; and persons who travel to or live in countries in which meningococcal disease is hyperendemic or epidemic (e.g., the "meningitis belt" of sub-Saharan Africa during the dry season [December–June]), particularly if their contact with local populations will be prolonged. Vaccination is required by the government of Saudi Arabia for all travelers to Mecca during the annual Hajj.

Meningococcal conjugate (MCV) vaccine is preferred for adults with any of the preceding indications who are aged 55 years or younger, although meningococcal polysaccharide vaccine (MPSV) is an acceptable alternative. Revaccination with MCV after 5 years might be indicated for adults previously vaccinated with MPSV who remain at increased risk for infection (e.g., persons residing in areas in which disease is epidemic).

12. Selected conditions for which *Haemophilus influenzae* type b (Hib) vaccine may be used

Hib vaccine generally is not recommended for persons aged 5 years and older. No efficacy data are available on which to base a recommendation concerning use of Hib vaccine for older children and adults. However, studies suggest good immunogenicity in persons who have sickle cell disease, leukemia, or HIV infection or who have had a splenectomy; administering 1 dose of vaccine to these persons is not contraindicated.

13. Immunocompromising conditions

Inactivated vaccines generally are acceptable (e.g., pneumococcal, meningococcal, and influenza [trivalent inactivated influenza vaccine]), and live vaccines generally are avoided in persons with immune deficiencies or immunocompromising conditions. Information on specific conditions is available at www.cdc.gov/vaccines/pubs/acip-list.htm.

Appendix A

Recommended and Minimum Ages and Intervals Between Doses of Routinely Recommended Vaccines[1]

Vaccine and dose number	Recommended age for this dose	Minimum age for this dose	Recommended interval to next dose	Minimum interval to next dose
Hepatitis B (HepB)-1[2]	Birth	Birth	1-4 months	4 weeks
HepB-2	1-2 months	4 weeks	2-17 months	8 weeks
HepB-3[3]	6-18 months	24 weeks	–	–
Diphtheria-tetanus-acellular pertussis (DTaP)-1[2]	2 months	6 weeks	2 months	4 weeks
DTaP-2	4 months	10 weeks	2 months	4 weeks
DTaP-3	6 months	14 weeks	6-12 months[4]	6 months[4,5]
DTaP-4	15-18 months	12 months	3 years	6 months[4]
DTaP-5	4-6 years	4 years	–	–
Haemophilus influenzae type b (Hib)-1[2,6]	2 months	6 weeks	2 months	4 weeks
Hib-2	4 months	10 weeks	2 months	4 weeks
Hib-3[7]	6 months	14 weeks	6-9 months[4]	8 weeks
Hib-4	12-15 months	12 months	–	–
Inactivated poliovirus (IPV)-1[2]	2 months	6 weeks	2 months	4 weeks
IPV-2	4 months	10 weeks	2-14 months	4 weeks
IPV-3	6-18 months	14 weeks	3-5 years	6 months
IPV-4	4-6 years	4 years	–	–
Pneumococcal conjugate (PCV)-1[6]	2 months	6 weeks	2 months	4 weeks
PCV-2	4 months	10 weeks	2 months	4 weeks
PCV-3	6 months	14 weeks	6 months	8 weeks
PCV-4	12-15 months	12 months	–	–
Measles-mumps-rubella (MMR)-1[8]	12-15 months	12 months	3-5 years	4 weeks
MMR-2[8]	4-6 years	13 months	–	–
Varicella (Var)-1[8]	12-15 months	12 months	3-5 years	12 weeks [9]
Var-2[8]	4-6 years	15 months	–	–
Hepatitis A (HepA)-1[2]	12-23 months	12 months	6-18 months[4]	6 months[4]
HepA-2	18-41 months	18 months	–	–
Influenza, Inactivated (TIV)[10]	6-59 months	6 months[11]	1 month	4 weeks
Influenza, Live attenuated (LAIV)[10]	–	2 years	1 month	4 weeks
Meningococcal Conjugate (MCV)	11-12 years	2 years	–	–
Meningococcal Polysaccharide (MPSV)-1	–	2 years	5 years[12]	5 years[12]
MPSV-2[13]	–	7 years	–	–
Tetanus-diphtheria (Td)	11-12 years	7 years	10 years	5 years
Tetanus-diphtheria-acellular pertussis (Tdap)[14]	≥11 years	10 years	–	–
Pneumococcal polysaccharide (PPSV)-1	–	2 years	5 years	5 years
PPSV-2[15]	–	7 years	–	–

Vaccine and dose number	Recommended age for this dose	Minimum age for this dose	Recommended interval to next dose	Minimum interval to next dose
Human papillomavirus (HPV)-1[16]	11-12 years	9 years	2 months	4 weeks
HPV-2	11-12 years (+2 months)	109 months	4 months	12 weeks
HPV-3[17]	11-12 years (+6 months)	114 months	–	–
Rotavirus (RV)-1[18]	2 months	6 weeks	2 months	4 weeks
RV-2	4 months	10 weeks	2 months	4 weeks
RV-3[19]	6 months	14 weeks	–	–
Zoster[20]	60 years	60 years	–	–

1 Use of licensed combination vaccines is preferred over separate injections of their equivalent component vaccines. (CDC. Combination vaccines for childhood immunization: recommendations of the Advisory Committee on Immunization Practices [ACIP], the American Academy of Pediatrics [AAP], and the American Academy of Family Physicians [AAFP]. *MMWR* 1999;48[No. RR-5]). When administering combination vaccines, the minimum age for administration is the oldest age for any of the individual components; the minimum interval between doses is equal to the greatest interval of any of the individual components.

2 Combination vaccines containing the Hepatitis B component are available (HepB-Hib, DTaP-HepB-IPV, HepA-HepB). These vaccines should not be administered to infants younger than 6 weeks of age because of the other components (i.e., Hib, DTaP, IPV, and HepA).

3 HepB-3 should be administered at least 8 weeks after HepB-2 and at least 16 weeks after HepB-1, and it should not be administered before age 24 weeks.

4 Calendar months.

5 The minimum recommended interval between DTaP-3 and DTaP-4 is 6 months. However, DTaP-4 need not be repeated if administered at least 4 months after DTaP-3.

6 For Hib and PCV, children receiving the first dose of vaccine at age 7 months of age or older require fewer doses to complete the series (CDC. Recommended childhood and adolescent immunization schedule – United States, 2006. *MMWR* 2005; 54 [Nos. 51 & 52]:Q1-Q4).

7 If PRP-OMP (Pedvax-Hib®, Merck Vaccine Division), was administered at 2 and 4 months of age a dose at 6 months of age is not required.

8 Combination measles-mumps-rubella-varicella (MMRV) vaccine can be used for children 12 months through 12 years of age. Also see footnote 9.

9 The minimum interval from Var-1 to Var-2 for persons beginning the series at 13 years or older is 4 weeks.

10 One dose of influenza vaccine per season is recommended for most people. Children younger than 9 years of age who are receiving influenza vaccine for the first time, or received only 1 dose the previous season (if it was their first vaccination season) should receive 2 doses this season.

11 The minimum age for inactivated influenza vaccine varies by vaccine manufacturer. Only Fluzone (manufactured by sanofi pasteur) is approved for children 6-35 months of age. The minimum age for Fluvirin (manufactured by Novartis) is 4 years. For Fluarix and FluLaval (manufactured by GlaxoSmithKline) and Afluria (manufactured by CSL Ltd), the minimum age is 18 years.

12 Some experts recommend a second dose of MPSV-3 years after the first dose for people at increased risk for meningococcal disease.

13 A second dose of meningococcal vaccine is recommended for people previously vaccinated with MPSV who remain at high risk for meningococcal disease. MCV is preferred when revaccinating persons aged 2-55 years, but a second dose of MPSV is acceptable. (CDC. Prevention and Control of Meningococcal Disease Recommendations of the Advisory Committee on Immunization Practices [ACIP]. *MMWR* 2005; 54: No. RR-7.)

14 Only one dose of Tdap is recommended. Subsequent doses should be administered as Td. If vaccination to prevent tetanus and/or diphtheria disease is required for children 7 through 9 years of age, Td should be administered (minimum age for Td is 7 years). For one brand of Tdap the minimum age is 11 years. The preferred interval between Tdap and a previous dose of Td is 5 years. In persons who have received a primary series of tetanus-toxoid containing vaccine, for management of a tetanus-prone wound, the minimum interval after a previous dose of any tetanus-containing vaccine is 5 years.

15 A second dose of PPSV is recommended for persons at highest risk for serious pneumococcal infection and those who are likely to have a rapid decline in pneumococcal antibody concentration. Revaccination 3 years after the previous dose can be considered for children at highest risk for severe pneumococcal infection who would be younger than 10 years of age at the time of revaccination. (CDC. Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunization Practices [ACIP]. *MMWR* 1997;46[No. RR-8]).

16 HPV is approved only for females 9-26 years of age.

17 HPV-3 should be administered at least 12 weeks after HPV-2 and at least 24 weeks after HPV-1, and it should not be administered before 114 months of age.

18 The first dose of RV must be administered at 6-14 weeks of age. The vaccine series should not be started after a child has reached 15 weeks of age. RV may be administered on the day a child reaches his or her 8 month birthday but not later, regardless of the number of doses administered previously.

19 If Rotarix (RV1) is administered as age appropriate, a third dose is not necessary.

20 Herpes zoster vaccine is approved as a single dose for persons 60 years and older with a history of varicella.

Adapted from Table 1, ACIP General Recommendations on Immunization: *MMWR* 2006;55(No. RR-15)

Summary of Recommendations for Childhood and Adolescent Immunization (Page 1 of 3)

Vaccine name and route	Schedule for routine vaccination and other guidelines (any vaccine can be given with another)	Schedule for catch-up vaccination and related issues	Contraindications and precautions (mild illness is not a contraindication)
Hepatitis B (HepB) *Give IM*	• Vaccinate all children age 0 through 18yrs. • Vaccinate all newborns with monovalent vaccine prior to hospital discharge. Give dose #2 at age 1–2m and the final dose at age 6–18m (the last dose in the infant series should not be given earlier than age 24wks). After the birth dose, the series may be completed using 2 doses of single-antigen vaccine or up to 3 doses of Comvax (ages 2m, 4m, 12–15m) or Pediarix (ages 2m, 4m, 6m), which may result in giving a total of 4 doses of hepatitis B vaccine. • **If mother is HBsAg-positive:** give the newborn HBIG + dose #1 within 12hrs of birth; complete series at age 6m or, if using Comvax, at age 12–15m. • **If mother's HBsAg status is unknown:** give the newborn dose #1 within 12hrs of birth. If mother is subsequently found to be HBsAg positive, give infant HBIG within 7d of birth and follow the schedule for infants born to HBsAg-positive mothers.	• Do not restart series, no matter how long since previous dose. • 3-dose series can be started at any age. • Minimum spacing between doses: 4wks between #1 and #2, 8wks between #2 and #3, and at least 16wks between #1 and #3 (e.g., 0-, 2-, 4m; 0-, 1-, 4m). **Special Notes on Hepatitis B Vaccine (HepB)** **Dosing of HepB:** Vaccine brands are interchangeable. For persons age 0 through 19yrs, give 0.5 mL of either Engerix-B or Recombivax HB. **Alternative dosing schedule for unvaccinated adolescents age 11 through 15yrs:** Give 2 doses Recombivax HB 1.0 mL (adult formulation) spaced 4–6m apart. (Engerix-B is not licensed for a 2-dose schedule.) **For preterm infants:** Consult ACIP hepatitis B recommendations (*MMWR* 2005; 54 [RR-16]).*	**Contraindication** Previous anaphylaxis to this vaccine or to any of its components. **Precaution** Moderate or severe acute illness.
DTaP, DT (Diphtheria, tetanus, acellular pertussis) *Give IM*	• Give to children at ages 2m, 4m, 6m, 15–18m, 4–6yrs. • May give dose #1 as early as age 6wks. • May give #4 as early as age 12m if 6m have elapsed since #3 and the child is unlikely to return at age 15–18m. • Do not give DTaP/DT to children age 7yrs and older. • If possible, use the same DTaP product for all doses.	• #2 and #3 may be given 4wks after previous dose. • #4 may be given 6m after #3. • If #4 is given before 4th birthday, wait at least 6m for #5 (age 4–6yrs). • If #4 is given after 4th birthday, #5 is not needed.	**Contraindications** • Previous anaphylaxis to this vaccine or to any of its components. • For DTaP/Tdap only: encephalopathy within 7d after DTP/DTaP. **Precautions** • Moderate or severe acute illness. • History of Arthus reaction following a prior dose of tetanus- and/or diphtheria-toxoid-containing vaccine, including MCV. • Guillain-Barré syndrome within 6wks after previous dose of tetanus toxoid-containing vaccine. • For DTaP only: Any of these events following a previous dose of DTP/DTaP: 1) temperature of 105°F (40.5°C) or higher within 48hrs; 2) continuous crying for 3hrs or more within 48hrs; 3) collapse or shock-like state within 48hrs; 4) convulsion with or without fever within 3d. • For DTaP/Tdap only: Unstable neurologic disorder. **Note:** Use of Td or Tdap is not contraindicated in pregnancy. At the provider's discretion, either vaccine may be administered during the 2nd or 3rd trimester.
Td, Tdap (Tetanus, diphtheria, acellular pertussis) *Give IM*	• Give 1-time Tdap dose to adolescents age 11–12yrs if 5yrs have elapsed since last dose DTaP; then boost every 10yrs with Td. • Give 1-time dose of Tdap to all adolescents who have not received previous Tdap. Special efforts should be made to give Tdap to persons age 11yrs and older who are – in contact with infants younger than age 12m. – healthcare workers with direct patient contact. • In pregnancy, when indicated, give Td or Tdap in 2nd or 3rd trimester. If not administered during pregnancy, give Tdap in immediate postpartum period.	• If never vaccinated with tetanus- and diphtheria-containing vaccine: give Td dose #1 now, dose #2 4wks later, and dose #3 6m after #2, then give booster every 10yrs. A 1-time Tdap may be substituted for any dose in the series, preferably as dose #1. For persons who previously received a Td booster, an interval of 2yrs or less between Td and Tdap may be used.	
Polio (IPV) *Give SC or IM*	• Give to children at ages 2m, 4m, 6–18m, 4–6yrs. • May give dose #1 as early as age 6wks. • Not routinely recommended for U.S. residents age 18yrs and older (except certain travelers).	• All doses should be separated by at least 4wks. • If dose #3 is given after 4th birthday, dose #4 is not needed.	**Contraindication** Previous anaphylaxis to this vaccine or to any of its components. **Precautions** • Moderate or severe acute illness. • Pregnancy.
Human papillomavirus (HPV) *Give IM*	• Give 3-dose series to girls at age 11–12yrs on a 0, 2, 6m schedule. (May be given as early as age 9yrs.) • Vaccinate all older girls and women (through age 26yrs) who were not previously vaccinated.	Minimum spacing between doses: 4wks between #1 and #2; 12 wks between #2 and #3. Overall, there must be at least 24wks between doses #1 and #3.	**Contraindication** Previous anaphylaxis to this vaccine or to any of its components. **Precautions** • Moderate or severe acute illness. • Pregnancy.

*This document was adapted from the recommendations of the Advisory Committee on Immunization Practices (ACIP). To obtain copies of the recommendations, call the CDC-INFO Contact Center at (800) 232-4636; visit CDC's website at www.cdc.gov/vaccines/pubs/ACIP-list.htm; or visit the Immunization Action Coalition (IAC) website at www.immunize.org/acip. This table is revised periodically. Visit IAC's website at www.immunize.org/childrules to make sure you have the most current version.

Adviser current issued by the Centers for Disease Control and Prevention, November 2008.

Summary of Recommendations for Childhood and Adolescent Immunization

Vaccine name and route	Schedule for routine vaccination and other guidelines (any vaccine can be given with another)	Schedule for catch-up vaccine administration and related issues	Contraindications and precautions (mild illness is not a contraindication)
Varicella (Var) (Chickenpox) *Give SC*	• Give dose #1 at age 12–15m. • Give dose #2 at age 4–6yrs. Dose #2 may be given earlier if at least 3m since dose #1. • Give a second dose to all older children and adolescents with history of only 1 dose. • MMRV may be used in children age 12m through 12yrs.	• If younger than age 13yrs, space dose #1 and #2 at least 3m apart. If age 13yrs or older, space at least 4wks apart. • May use as postexposure prophylaxis if given within 5d. • If Var and either MMR, LAIV, and/or yellow fever vaccine are not given on the same day, space them at least 28d apart.	**Contraindications** • Previous anaphylaxis to this vaccine or to any of its components. • Pregnancy or possibility of pregnancy within 4wks. • Children on high-dose immunosuppressive therapy or who are immunocompromised because of malignancy and primary or acquired cellular immunodeficiency, including HIV/AIDS (although vaccination may be considered if CD4+ T-lymphocyte percentages are either 15% or greater in children ages 1 through 8yrs or 200 cells/mL or greater in children age 9yrs or older). **Precautions** • Moderate or severe acute illness. • If blood, plasma, and/or immune globulin (IG or VZIG) were given in past 11m, see ACIP statement *General Recommendations on Immunization** regarding time to wait before vaccinating. **Note:** For patients with humoral immunodeficiency or leukemia, see ACIP recommendations*.
MMR (Measles, mumps, rubella) *Give SC*	• Give dose #1 at age 12–15m. • Give dose #2 at age 4–6yrs. Dose #2 may be given earlier if at least 4wks since dose #1. • Give a second dose to all older children and teens with history of only 1 dose. • MMRV may be used in children age 12m through 12yrs.	• If MMR and either Var, LAIV, and/or yellow fever vaccine are not given on the same day, space them at least 28d apart. • When using MMR for both doses, minimum interval is 4wks. • When using MMRV for both doses, minimum interval is 3m. • Within 72hrs of measles exposure, give 1 dose of MMR as postexposure prophylaxis to susceptible healthy children age 12m and older.	**Contraindications** • Previous anaphylaxis to this vaccine or to any of its components. • Pregnancy or possibility of pregnancy within 4wks. • Severe immunodeficiency (e.g., hematologic and solid tumors; receiving chemotherapy; congenital immunodeficiency; long-term immunosuppressive therapy, or severely symptomatic HIV). Note: HIV infection is NOT a contraindication to MMR for children who are not severely immunocompromised (consult ACIP MMR recommendations [*MMWR* 1998;47 [RR-8] for details*). **Precautions** • Moderate or severe acute illness. • If blood, plasma, or immune globulin given in past 11m, see ACIP statement *General Recommendations on Immunization** regarding time to wait before vaccinating. • History of thrombocytopenia or thrombocytopenic purpura. **Note:** MMR is not contraindicated if a TST (tuberculosis skin test) was recently applied. If TST and MMR are not given on same day, delay TST for at least 4wks after MMR.
Influenza Trivalent inactivated influenza vaccine (TIV) *Give IM* Live attenuated influenza vaccine (LAIV) *Give intranasally*	• Vaccinate all children and teens age 6m through 18yrs, as well as all household contacts of infants and children through age 59m (4yrs 11m). • Vaccinate persons age 19yrs and older who – have a risk factor (e.g., pregnancy, heart or lung disease, renal, hepatic, hematologic, or metabolic disorder [including diabetes], immunosuppression, or have a condition that compromises respiratory function or the handling of respiratory secretions or that can increase the risk of aspiration) or live in a chronic-care facility. – live or work with at-risk people as listed above. • All other persons who want to reduce the likelihood of becoming ill with influenza or of spreading it to others. • LAIV may be given to healthy, non-pregnant persons age 2–49yrs. • Give 2 doses to first-time vaccinees age 6m through 8yrs, spaced 4wks apart. • For TIV, give 0.25 mL dose to children age 6–35m and 0.5 mL dose if age 3yrs and older.		**Contraindications** • Previous anaphylaxis to this vaccine, to any of its components, or to eggs. • For LAIV only: Pregnancy, asthma, reactive airways disease, or other chronic disorder of the pulmonary or cardiovascular systems; an underlying medical condition, including metabolic diseases such as diabetes, renal dysfunction, and hemoglobinopathies; known or suspected immune deficiency diseases or immunosuppressed states; for children younger than age 5yrs, possible reactive airways disease (e.g., recurrent wheezing or a wheezing episode within the past 12m). **Precautions** • Moderate or severe acute illness. • History of Guillain-Barré syndrome within 6wks of a previous influenza vaccination. **Note:** If LAIV and either MMR, Var, and/or yellow fever vaccine are not given on the same day, space them at least 28d apart.
Rotavirus (RV) *Give orally*	• Rotarix (RV1): give at age 2m, 4m • RotaTeq (RV5): give at age 2m, 4m, 6m • May give dose #1 as early as age 6wks. • Give dose #3 no later than age 8m 0 days.	• Do not begin series in infants older than age 15wks 0 days. • Intervals between doses may be as short as 4wks. • If prior vaccination included use of different or unknown brand(s), a total of 3 doses should be given.	**Contraindication** Previous anaphylaxis to this vaccine or to any of its components, including latex for RV1. **Precautions** • Moderate or severe acute illness. • Altered immunocompetence. • Moderate to severe acute gastroenteritis or chronic gastrointestinal disease. • History of intussusception.

Summary of Recommendations for Childhood and Adolescent Immunization

Vaccine name and route	Schedule for routine vaccination and other guidelines (any vaccine can be given with another)	Schedule for catch-up vaccination and related issues	Contraindications and precautions (mild illness is not a contraindication)
Hib (*Haemophilus influenzae* type b) *Give IM*	• ActHib (PRP-T): give at age 2m, 4m, 6m, 12–15m (booster dose). • PedvaxHIB or Comvax (containing PRP-OMP): give at age 2m, 4m, 12–15m (booster dose). • Dose #1 of Hib vaccine should not be given earlier than age 6wks. • The last dose (booster dose) is given no earlier than age 12m and a minimum of 8wks after the previous dose. • Hib vaccines are interchangeable; however, if different brands of Hib vaccines are administered for dose #1 and dose #2, a total of 3 doses are necessary to complete the primary series in infants. • Any Hib vaccine may be used for the booster dose. • Hib is not routinely given to children age 5yrs and older.	**All Hib vaccines:** • If #1 was given at 12–14m, give booster in 8wks. • Give only 1 dose to unvaccinated children from age 15 through 59m. **ActHib:** • #2 and #3 may be given 4wks after previous dose. • If #1 was given at age 7–11m, only 3 doses are needed; #2 is given 4–8wks after #1, then boost at age 12–15m (wait at least 8wks after dose #2). **PedvaxHIB and Comvax:** • #2 may be given 4wks after dose #1.	**Contraindications** • Previous anaphylaxis to this vaccine or to any of its components. • Age younger than 6wks. **Precaution** Moderate or severe acute illness.
Pneumo. conjugate (PCV) *Give IM*	• Give at ages 2m, 4m, 6m, 12–15m. • Dose #1 may be given as early as age 6wks. • Give 1 dose to unvaccinated healthy children age 24–59m. • For high-risk** children ages 24–59m, give 2 doses at least 8wks apart if previous vaccinations were fewer than 3 doses, or give 1 dose if previously received 3 doses. • PCV is not routinely given to children age 5yrs and older. ****High-risk:** Those with sickle cell disease; anatomic/functional asplenia; chronic cardiac, pulmonary, or renal disease; diabetes; cerebrospinal fluid leaks; HIV infection; immunosuppression; diseases associated with immunosuppressive and/or radiation therapy; or who have or will have a cochlear implant.	• For age 7–11m: If history of 0–2 doses, give additional doses 4wks apart with no more than 3 total doses by age 12m; then give booster 8wks later. • For age 12–23m: If 0–1 dose before age 12m, give 2 doses at least 8wks apart. If 2–3 doses before age 12m, give 1 dose at least 8wks after previous dose. • For age 24–59m: If patient has had no previous doses, or has a history of 1–3 doses given before age 12m but no booster dose, or has a history of only 1 dose given at age 12–23m, give 1 dose now.	**Contraindication** Previous anaphylaxis to this vaccine or to any of its components. **Precaution** Moderate or severe acute illness.
Pneumo. polysacch. (PPSV) *Give IM or SC*	• Give 1 dose at least 8wks after final dose of PCV to high-risk children age 2yrs and older. • For children who are immunocompromised or have sickle cell disease or functional or anatomic asplenia, give a 2nd dose of PPSV 5yrs after previous PPSV (consult ACIP PPSV recommendations at http://www.cdc.gov/vaccines/pubs/ACIP-list.htm[8]).		**Contraindication** Previous anaphylaxis to this vaccine or to any of its components. **Precaution** Moderate or severe acute illness.
Hepatitis A (HepA) *Give IM*	• Give 2 doses to all children at age 1yr (12–23m) spaced 6m apart. • Vaccinate all previously unvaccinated children and adolescents age 2 years and older who - Live in a state, county, or community with a routine vaccination program already in place for children age 2yrs and older. - Travel anywhere except U.S., W. Europe, N. Zealand, Australia, Canada, or Japan. - Wish to be protected from HAV infection. - Have chronic liver disease, clotting factor disorder, or are MSM adolescents. - Are injecting or non-injecting drug users.	• Minimum interval between doses is 6m. • Children who are not fully vaccinated by age 2yrs can be vaccinated at subsequent visits. • Consider routine vaccination of children age 2yrs and older in areas with no existing program. • Give 1 dose as postexposure prophylaxis to incompletely vaccinated children age 12m and older who have recently (during the past 2wks) been exposed to hepatitis A virus.	**Contraindication** Previous anaphylaxis to this vaccine or to any of its components. **Precautions** • Moderate or severe acute illness. • Pregnancy.
Meningococcal conjugate (MCV) *Give IM* **polysaccharide** (MPSV) *Give SC*	• Give 1-time dose of MCV to adolescents age 11 through 18yrs. • Vaccinate all college freshmen living in dorms who have not been vaccinated. • Vaccinate all children age 2yrs and older who have any of the following risk factors (MCV is preferable to MPSV): - Anatomic or functional asplenia, or terminal complement component deficiency. - Travel to or reside in countries in which meningococcal disease is hyperendemic or epidemic (e.g., the "meningitis belt" of Sub-Saharan Africa).	If previously vaccinated with MPSV and risk continues, give MCV 5yrs after MPSV.	**Contraindication** Previous anaphylaxis to this vaccine or to any of its components, including diphtheria toxoid (for MCV). **Precautions** • Moderate or severe acute illness. • For MCV only: history of Guillain-Barré syndrome (GBS).

Summary of Recommendations for Adult Immunization

Vaccine name and route	For whom vaccination is recommended	Schedule for vaccine administration (any vaccine can be given with another)	Contraindications and precautions (mild illness is not a contraindication)
Influenza Trivalent inactivated influenza vaccine (TIV) *Give IM* Live attenuated influenza vaccine (LAIV) *Give intranasally*	• All persons who want to reduce the likelihood of becoming ill with influenza or of spreading it to others. • Persons age 50yrs and older. [TIV only] • Persons with medical problems (e.g., heart or lung disease, renal, hepatic, hematologic, or metabolic disorder [including diabetes], immunosuppression). [TIV only] • Persons with any condition that compromises respiratory function or the handling of respiratory secretions or that can increase the risk of aspiration (e.g., cognitive dysfunction, spinal cord injury, seizure disorder, or other neuromuscular disorder). [TIV only] • Persons living in chronic care facilities. [TIV only] • Persons who work or live with high-risk people. • Women who will be pregnant during the influenza season (December–spring). [If currently pregnant, TIV only] • All healthcare personnel and other persons who provide direct care to high-risk people. • Household contacts and out-of-home caregivers of children age 0–59m. • Travelers at risk for complications of influenza who go to areas where influenza activity exists or who may be among people from areas of the world where there is current influenza activity (e.g., on organized tours). [TIV only] • Students or other persons in institutional settings (e.g., residents of dormitories or correctional facilities). **Note:** LAIV may not be given to some of the persons listed to the left; see contraindications listed in far right column.	• Give 1 dose every year in the fall or winter. • Begin vaccination services as soon as vaccine is available and continue until the supply is depleted. • Continue to give vaccine to unvaccinated adults throughout the influenza season (including when influenza activity is present in the community) and at other times when the risk of influenza exists. • If 2 or more of the following live virus vaccines are to be given—LAIV, MMR, Var, and/or yellow fever vaccine—they should be given on the same day. If they are not, space them by at least 28d.	**Contraindications** • Previous anaphylactic reaction to this vaccine, to any of its components, or to eggs. • For LAIV only, age 50 years or older, pregnancy, asthma, reactive airway disease or other chronic disorder of the pulmonary or cardiovascular system; an underlying medical condition, including metabolic disease such as diabetes, renal dysfunction, and hemoglobinopathy; a known or suspected immune deficiency disease or immunosuppressed state. **Precautions** • Moderate or severe acute illness. • History of Guillain-Barré syndrome (GBS) within 6wks of previous influenza vaccination.
Pneumococcal poly-saccharide (PPSV) *Give IM or SC*	• Persons age 65yrs and older. • Persons who have chronic illness or other risk factors, including chronic cardiac or pulmonary disease, chronic liver disease, alcoholism, diabetes, CSF leaks, cigarette smoking, as well as people living in special environments or social settings (including Alaska Natives and certain American Indian populations age 50 through 64 years if recommended by local public health authorities). • Those at highest risk of fatal pneumococcal infection, including persons who - have anatomic asplenia, functional asplenia, or sickle cell disease - have an immunocompromising condition, including HIV infection, leukemia, lymphoma, Hodgkin's disease, multiple myeloma, generalized malignancy, chronic renal failure, or nephrotic syndrome - are receiving immunosuppressive chemotherapy (including corticosteroids) - have received an organ or bone marrow transplant - are candidates for or recipients of cochlear implants.	• Give 1 dose if unvaccinated or if previous vaccination history is unknown. • Give a 1-time revaccination at least 5yrs after 1st dose to persons - age 65yrs and older if the 1st dose was given prior to age 65yrs - at highest risk of fatal pneumococcal infection or rapid antibody loss (see the 3rd bullet in the box to left for listings of persons at highest risk)	**Contraindication** Previous anaphylactic reaction to this vaccine or to any of its components. **Precaution** Moderate or severe acute illness.
Zoster (shingles) (Zos) *Give SC*	• Persons age 60yrs and older.	• Give 1-time dose if unvaccinated, regardless of previous history of herpes zoster (shingles) or chickenpox.	**Contraindications** • Previous anaphylactic reaction to any component of zoster vaccine (e.g., gelatin & neomycin). • Primary cellular or acquired immunodeficiency. • Pregnancy. **Precaution** Moderate or severe acute illness.

*This document was adapted from the recommendations of the Advisory Committee on Immunization Practices (ACIP). To obtain copies of these recommendations, call the CDC-INFO Contact Center at (800) 232-4636; visit CDC's website at www.cdc.gov/vaccines/pubs/ACIP-list.htm; or visit the Immunization Action Coalition (IAC) website at www.immunize.org/acip. This table is revised periodically. Visit IAC's website at www.immunize.org/adultrules to make sure you have the most current version.

Technical content reviewed by the Centers for Disease Control and Prevention. November 2008.

www.immunize.org/catg.d/p2011.pdf • Item #P2011 (11/08)

Immunization Action Coalition • 1573 Selby Avenue • Saint Paul, MN 55104 • (651) 647-9009 • www.immunize.org • www.vaccineinformation.org • admin@immunize.org

Summary of Recommendations for Adult Immunization (continued)

Vaccine name and route	For whom vaccination is recommended	Schedule for vaccine administration (any vaccine can be given with another)	Contraindications and precautions (mild illness is not a contraindication)
Hepatitis B (HepB) *Give IM* Brands may be used interchangeably.	• All persons through age 18yrs. • All adults wishing to be protected from hepatitis B virus infection. • High-risk persons, including household contacts and sex partners of HBsAg-positive persons; injecting drug users; sexually active persons not in a long-term, mutually monogamous relationship; men who have sex with men; persons with HIV; persons seeking evaluation or treatment for an STD; patients receiving hemodialysis and patients with renal disease that may result in dialysis; healthcare personnel and patients with renal disease that may result in dialysis; healthcare personnel and public safety workers who are exposed to blood; clients and staff of institutions for the developmentally disabled; inmates of long-term correctional facilities; and certain international travelers. • Persons with chronic liver disease. **Note:** Provide serologic screening for immigrants from endemic areas. If patient is chronically infected, assure appropriate disease management. Screen sex partners and household members; give HepB at the same visit if not already vaccinated.	• Give 3 doses on a 0, 1, 6m schedule. • Alternative timing options for vaccination include 0, 2, 4m and 0, 1, 4m. • There must be at least 4wks between doses #1 and #2, and at least 8wks between doses #2 and #3. Overall, there must be at least 16wks between doses #1 and #3. • **Schedule for those who have fallen behind:** If the series is delayed between doses, DO NOT start the series over. Continue from where you left off. For Twinrix® (hepatitis A and B combination vaccine [GSK]) for patients age 18yrs and older only: give 3 doses on a 0, 1, 6m schedule. There must be at least 4wks between doses #1 and #2, and at least 5m between doses #2 and #3. An alternative schedule can also be used at 0, 7d, 21–30d, and a booster at 12m.	**Contraindication** Previous anaphylactic reaction to this vaccine or to any of its components. **Precaution** Moderate or severe acute illness.
Hepatitis A (HepA) *Give IM* Brands may be used interchangeably.	• All persons wishing to be protected from hepatitis A virus (HAV) infection. • Persons who travel or work anywhere EXCEPT the U.S., Western Europe, New Zealand, Australia, Canada, and Japan. • Persons with chronic liver disease; injecting and non-injecting drug users; men who have sex with men; people who receive clotting-factor concentrates; persons who work with HAV in experimental lab settings (not routine medical laboratories); food handlers when health authorities or private employers determine vaccination to be appropriate. • Unvaccinated adults age 40yrs or younger with recent (within 2 wks) exposure to HAV. For persons older than age 40yrs with recent (within 2 wks) exposure to HAV, immune globulin is preferred over HepA vaccine.	• Give 2 doses. • The minimum interval between doses #1 and #2 is 6m. • If dose #2 is delayed, do not repeat dose #1. Just give dose #2.	**Contraindication** Previous anaphylactic reaction to this vaccine or to any of its components. **Precautions** • Moderate or severe acute illness. • Safety during pregnancy has not been determined, so benefits must be weighed against potential risk.
Td, Tdap (Tetanus, diphtheria, pertussis) *Give IM*	• All adults who lack written documentation of a primary series consisting of at least 3 doses of tetanus- and diphtheria-toxoid-containing vaccine. • A booster dose of tetanus- and diphtheria-toxoid-containing vaccine may be needed for wound management as early as 5yrs after receiving a previous dose, so consult ACIP recommendations.* • Using tetanus toxoid (TT) instead of Td or Tdap is not recommended. • In pregnancy, when indicated, give Td or Tdap in 2nd or 3rd trimester. If not administered during pregnancy, give Tdap in immediate postpartum period. **For Tdap only:** • All adults younger than age 65yrs who have not already received Tdap. • Adults in contact with infants younger than age 12m (e.g., parents, grandparents younger than age 65yrs, childcare providers, healthcare personnel) who have not received a dose of Tdap should be prioritized for vaccination. • Healthcare personnel who work in hospitals or ambulatory care settings and have direct patient contact and who have not received Tdap.	• For persons who are unvaccinated or behind, complete the primary series with Td (spaced at 0, 1–2m, 6–12m intervals). One-time dose of Tdap may be used for any dose if younger than age 65yrs. • Give Td booster every 10yrs after the primary series has been completed. For adults younger than age 65yrs, a 1-time dose of Tdap is recommended to replace the next Td. • Intervals of 2yrs or less between Td and Tdap may be used. **Note:** The two Tdap products are licensed for different age groups: Adacel™ (sanofi) for use in persons age 11–64yrs and Boostrix® (GSK) for use in persons age 10–18yrs.	**Contraindications** • Previous anaphylactic reaction to this vaccine or to any of its components. • For Tdap only, history of encephalopathy within 7d following DTP/DTaP. **Precautions** • Moderate or severe acute illness. • GBS within 6wks of receiving a previous dose of tetanus-toxoid-containing vaccine. • Unstable neurologic condition. • History of Arthus reaction following a previous dose of tetanus- and/or diphtheria-toxoid-containing vaccine, including MCV. **Note:** Use of Td/Tdap is not contraindicated in pregnancy. Either vaccine may be given during trimester #2 or #3 at the provider's discretion.
Polio (IPV) *Give IM or SC*	Not routinely recommended for U.S. residents age 18yrs and older. **Note:** Adults living in the U.S. who never received or completed a primary series of polio vaccine need not be vaccinated unless they intend to travel to areas where exposure to wild-type virus is likely (i.e., India, Pakistan, Afghanistan, and Nigeria). Previously vaccinated adults can receive 1 booster dose if traveling to polio endemic areas.	• Refer to ACIP recommendations* regarding unique situations, schedules, and dosing information.	**Contraindication** Previous anaphylactic or neurologic reaction to this vaccine or to any of its components. **Precautions** • Moderate or severe acute illness. • Pregnancy.

Summary of Recommendations for Adult Immunization (continued)

Vaccine name and route	For whom vaccination is recommended	Schedule for vaccine administration (any vaccine can be given with another)	Contraindications and precautions (mild illness is not a contraindication)
Varicella (Var) (Chickenpox) *Give SC*	• All adults without evidence of immunity. **Note:** Evidence of immunity is defined as written documentation of 2 doses of varicella vaccine; a history of varicella disease or herpes zoster (shingles) based on healthcare-provider diagnosis; laboratory evidence of immunity; laboratory confirmation of disease; and/or birth in the U.S. before 1980, with the exceptions that follow. Healthcare personnel (HCP) and pregnant women born in the U.S. before 1980 who do not meet any of the criteria above should be tested. If they are not immune, give the first dose of varicella vaccine immediately (HCP) or postpartum and before hospital discharge (pregnant women). Give the second dose 4–8 wks later. Routine post-vaccination testing is not recommended.	• Give 2 doses. • Dose #2 is given 4–8wks after dose #1. • If the second dose is delayed, do not repeat dose #1. Just give dose #2. • If 2 or more of the following live virus vaccines are to be given—LAIV, MMR, Var, and/or yellow fever vaccine—they should be given on the same day. If they are not, space them by at least 28d. • May use as postexposure prophylaxis if given within 5d.	**Contraindications** • Previous anaphylactic reaction to this vaccine or to any of its components. • Pregnancy or possibility of pregnancy within 4wks. • Persons on high-dose immunosuppressive therapy or who are immunocompromised because of malignancy and primary or acquired cellular immunodeficiency, including HIV/AIDS (although vaccination may be considered if CD4+ T-lymphocyte counts are greater than or equal to 200 cells/μL. See *MMWR* 2007;56,RR-4). **Precautions** • Moderate or severe acute illness. • If blood, plasma, and/or immune globulin (IG or VZIG) were given in past 11m, see ACIP statement *General Recommendations on Immunization** regarding time to wait before vaccinating.
Meningococcal Conjugate vaccine (MCV) *Give IM* Polysaccharide vaccine (MPSV) *Give SC*	• All persons age 11 through 18yrs. • College freshmen living in a dormitory. • Persons with anatomic or functional asplenia or with a terminal-complement component deficiency. • Persons who travel to or reside in countries in which meningococcal disease is hyperendemic or epidemic (e.g., the "meningitis belt" of Sub-Saharan Africa). • Microbiologists routinely exposed to isolates of *N. meningitidis*.	• Give 1 dose. • If previous vaccine was MPSV, revaccinate after 3yrs if risk continues. • Revaccination after MCV is not recommended. • MCV is preferred over MPSV for persons age 55yrs and younger, although MPSV is an acceptable alternative.	**Contraindication** Previous anaphylactic or neurologic reaction to this vaccine or to any of its components, including diphtheria toxoid (for MCV). **Precautions** • Moderate or severe acute illness. • For MCV only, history of Guillain-Barré syndrome (GBS).
MMR (Measles, mumps, rubella) *Give SC*	• Persons born in 1957 or later (especially those born outside the U.S.) should receive at least 1 dose of MMR if there is no serologic proof of immunity or documentation of a dose given on or after the first birthday. • Persons in high-risk groups, such as healthcare personnel (paid, unpaid, or volunteer), students entering college and other post–high school educational institutions, and international travelers, should receive a total of 2 doses. • Persons born before 1957 are usually considered immune, but proof of immunity (serology or vaccination) may be desirable for healthcare personnel. • Women of childbearing age who do not have acceptable evidence of rubella immunity or vaccination.	• Give 1 or 2 doses (see criteria in 1st and 2nd bullets in box to left). • If dose #2 is recommended, give it no sooner than 4wks after dose #1. • If a pregnant woman is found to be rubella susceptible, give 1 dose of MMR postpartum. • If 2 or more of the following live virus vaccines are to be given—LAIV, MMR, Var, and/or yellow fever vaccine—they should be given on the same day. If they are not, space them by at least 28d. • Within 72hrs of measles exposure, give 1 dose as postexposure prophylaxis to susceptible adults.	**Contraindications** • Previous anaphylactic reaction to this vaccine or to any of its components. • Pregnancy or possibility of pregnancy within 4wks. • Severe immunodeficiency (e.g., hematologic and solid tumors; receiving chemotherapy; congenital immunodeficiency; long-term immunosuppressive therapy; or severely symptomatic HIV.) **Note:** HIV infection is NOT a contraindication to MMR for those who are not severely immunocompromised (i.e., CD4+ T-lymphocyte counts are greater than or equal to 200 cells/μL). **Precautions** • Moderate or severe acute illness. • If blood, plasma, and/or immune globulin were given in past 11m, see ACIP statement *General Recommendations on Immunization** regarding time to wait before vaccinating. • History of thrombocytopenia or thrombocytopenic purpura. **Note:** If TST (tuberculosis skin test) and MMR are both needed but not given on same day, delay TST for 4–6wks after MMR.
Human papillomavirus (HPV) *Give IM*	All previously unvaccinated women through age 26yrs.	• Give 3 doses on a 0, 2, 6m schedule. • There must be at least 4wks between doses #1 and #2 and at least 12wks between doses #2 and #3. Overall, there must be at least 24wks between doses #1 and #3.	**Contraindication** Previous anaphylactic reaction to this vaccine or to any of its components. **Precautions** • Moderate or severe acute illness. • Data on vaccination in pregnancy are limited. Vaccination should be delayed until after completion of the pregnancy.

Suggested intervals between administration of **immune globulin preparations** and **measles-** or **varicella-containing vaccine**

Product / Indication	Dose, including mg immunoglobulin G (IgG)/kg body weight	Recommended interval before measles or varicella-containing[1] vaccine administration
RSV monoclonal antibody (Synagis™)[2]	15 mg/kg intramuscularly (IM)	None
Tetanus IG (TIG)	250 units (10 mg IgG/kg) IM	3 months
Hepatitis A IG		
Contact prophylaxis	0.02 mL/kg (3.3 mg IgG/kg) IM	3 months
International travel	0.06 mL/kg (10 mg IgG/kg) IM	3 months
Hepatitis B IG (HBIG)	0.06 mL/kg (10 mg IgG/kg) IM	3 months
Rabies IG (RIG)	20 IU/kg (22 mg IgG/kg) IM	4 months
Measles prophylaxis IG		
Standard (i.e., nonimmunocompromised) contact	0.25 mL/kg (40 mg IgG/kg) IM	5 months
Immunocompromised contact	0.5 mL/kg (80 mg IgG/kg) IM	6 months
Blood transfusion		
Red blood cells (RBCs), washed	10 mL/kg negligible IgG/kg intervenously (IV)	None
RBCs, adenine-saline added	10 mL/kg (10 mg IgG/kg) IV	3 months
Packed RBCs (Hct 65%)	10 mL/kg (60 mg IgG/kg) IV	6 months
Whole blood (Hct 35%-50%)[3]	10 mL/kg (80-100 mg IgG/kg) IV	6 months
Plasma/platelet products	10 mL/kg (160 mg IgG/kg) IV	7 months
Cytomegalovirus intravenous immune globulin (IGIV)	150 mg/kg maximum	6 months
IGIV		
Replacement therapy for immune deficiencies[4]	300-400 mg/kg IV[3]	8 months
Immune thrombocytopenic purpura	400 mg/kg IV	8 months
Immune thrombocytopenic purpura	1,000 mg/kg IV	10 months
Immune thrombocytopenic purpura / Kawasaki disease	1.6-2 g/kg IV	11 months
Postexposure varicella prophylaxis[5]	400 mg/kg IV	8 months

This table is not intended for determining the correct indications and dosages for using antibody-containing products. Unvaccinated persons might not be fully protected against measles during the entire recommended interval, and additional doses of immune globulin or measles vaccine might be indicated after measles exposure. Concentrations of measles antibody in an immune globulin preparation can vary by manufacturer's lot. Rates of antibody clearance after receipt of an immune globulin preparation also might vary. Recommended intervals are extrapolated from an estimated half-life of 30 days for passively acquired antibody and an observed interference with the immune response to measles vaccine for 5 months after a dose of 80 mg IgG/kg.

1 "Varicella-containing vaccine," as used here, does not include zoster vaccine. Zoster vaccine may be given with antibody-containing blood products.

2 Contains antibody only to respiratory syncytial virus

3 Assumes a serum IgG concentration of 16 mg/mL.

4 Measles and varicella vaccinations are recommended for children with asymptomatic or mildly symptomatic human immunodeficiency virus (HIV) infection, but are contraindicated for persons with severe immunosuppression from HIV or any other immunosuppressive disorder.

5 The investigational product VariZIG, similar to licensed VZIG, is a purified human immune globulin preparation made from plasma containing high levels of anti-varicella anbtibodies (immunoglobulin class G [IgG]). When indicated, health-care providers should make every effort to obtain and administer VariZIG. In situations in which administration of VariZIG does not appear possible within 96 hours of exposure, administration of immune globulin intravenous (IGIV) should be considered as an alternative. IGIV also should be administered within 96 hours of exposure. Although licensed IGIV preparations are known to contain anti-varicella antibody titers, the titer of any specific lot of IGIV that might be available is uncertain because IGIV is not routinely tested for antivaricella antibodies. The recommended IGIV dose for postexposure prophylaxis of varicella is 400 mg/kg, administered once. For a pregnant woman who cannot receive VariZIG within 96 hours of exposure, clinicians can choose either to administer IGIV or closely monitor the woman for signs and symptoms of varicella and institute treatment with acyclovir if illness occurs. (CDC. A new product for postexposure prophylaxis available under an investigational new drug application expanded access protocol. *MMWR* 2006;55:209-10.)

Healthcare Personnel Vaccination Recommendations

Vaccine	Recommendations in brief
Hepatitis B	Give 3-dose series (dose #1 now, #2 in 1 month, #3 approximately 5 months after #2). Give IM. Obtain anti-HBs serologic testing 1–2 months after dose #3.
Influenza	Give 1 dose of TIV or LAIV annually. Give TIV intramuscularly or LAIV intranasally.
MMR	For healthcare personnel (HCP) born in 1957 or later without serologic evidence of immunity or prior vaccination, give 2 doses of MMR, 4 weeks apart. For HCP born prior to 1957, see below. Give SC.
Varicella (chickenpox)	For HCP who have no serologic proof of immunity, prior vaccination, or history of varicella disease, give 2 doses of varicella vaccine, 4 weeks apart. Give SC.
Tetanus, diphtheria, pertussis	Give all HCP a Td booster dose every 10 years, following the completion of the primary 3-dose series. Give a 1-time dose of Tdap to all HCP younger than age 65 years with direct patient contact. Give IM.
Meningococcal	Give 1 dose to microbiologists who are routinely exposed to isolates of *N. meningitidis*.

Hepatitis A, typhoid, and polio vaccines are not routinely recommended for HCP who may have on-the-job exposure to fecal material.

Hepatitis B

Healthcare personnel (HCP) who perform tasks that may involve exposure to blood or body fluids should receive a 3-dose series of hepatitis B vaccine at 0-, 1-, and 6-month intervals. Test for hepatitis B surface antibody (anti-HBs) to document immunity 1–2 months after dose #3.

- If anti-HBs is at least 10 mIU/mL (positive), the patient is immune. No further serologic testing or vaccination is recommended.
- If anti-HBs is less than 10 mIU/mL (negative), the patient is unprotected from hepatitis B virus (HBV) infection; revaccinate with a 3-dose series. Retest anti-HBs 1–2 months after dose #3.
  - If anti-HBs is positive, the patient is immune. No further testing or vaccination is recommended.
  - If anti-HBs is negative following 6 doses of vaccine, the patient is a non-responder.

For non-responders: HCP who are non-responders should be considered susceptible to HBV and should be counseled regarding precautions to prevent HBV infection and the need to obtain HBIG prophylaxis for any known or probable parenteral exposure to hepatitis B surface antigen (HBsAg)-positive blood.[1] It is also possible that non-responders are persons who are HBsAg positive. Testing should be considered. HCP found to be HBsAg positive should be counseled and medically evaluated.

Note: Anti-HBs testing is not recommended routinely for previously vaccinated HCP who were not tested 1–2 months after their original vaccine series. These HCP should be tested for anti-HBs when they have an exposure to blood or body fluids. If found to be anti-HBs negative, the HCP should be treated as if susceptible.[1]

Influenza

Trivalent (Inactivated) Influenza Vaccine (TIV): May give to any HCP.
Live, Attenuated Influenza Vaccine (LAIV): May give to any non-pregnant healthy HCP age 49 years and younger.

1. All HCP should receive annual influenza vaccine. Groups that should be targeted include all personnel (including volunteers) in hospitals, outpatient, and home-health settings who have any patient contact.
2. TIV is preferred over LAIV for HCP who are in close contact with severely immunosuppressed persons (e.g., stem cell transplant patients) when patients require a protective environment.

Measles, Mumps, Rubella (MMR)

HCP who work in medical facilities should be immune to measles, mumps, and rubella.

- HCP born in 1957 or later can be considered immune to measles, mumps, or rubella only if they have documentation of (a) physician-diagnosed measles or mumps disease; or (b) laboratory evidence of measles, mumps, or rubella immunity (HCP who have an "indeterminate" or "equivocal" level of immunity upon testing should be considered nonimmune); or (c) appropriate vaccination against measles, mumps, and rubella (i.e., administration on or after the first birthday of two doses of live measles and mumps vaccines separated by 28 days or more, and at least one dose of live rubella vaccine).
- Although birth before 1957 generally is considered acceptable evidence of measles, mumps, and rubella immunity, healthcare facilities should consider recommending a dose of MMR vaccine (two doses during a mumps outbreak) to unvaccinated HCP born before 1957 who are in either of the following categories: (a) do not have a history of physician-diagnosed measles and mumps disease or laboratory evidence of measles and mumps immunity and (b) do not have laboratory evidence of rubella immunity.

Varicella

It is recommended that all HCP be immune to varicella. Evidence of immunity in HCP includes documentation of 2 doses of varicella vaccine given at least 28 days apart, history of varicella or herpes zoster based on physician diagnosis, laboratory evidence of immunity, or laboratory confirmation of disease.

Tetanus/Diphtheria/Pertussis (Td/Tdap)

All adults who have completed a primary series of a tetanus/diphtheria-containing product (DTP, DTaP, DT, Td) should receive Td boosters every 10 years. As soon as feasible, HCP younger than age 65 years with direct patient contact should be given a 1-time dose of Tdap, with priority given to those having contact with infants younger than age 12 months.

Meningococcal

Vaccination is recommended for microbiologists who are routinely exposed to isolates of *N. meningitidis*. Use of MCV4 is preferred for persons younger than age 56 years; give IM. If MCV4 is unavailable, MPSV is an acceptable alternative for HCP younger than age 56 years. Use of MPSV is recommended for HCP older than age 55; give SC.

References

1. See Table 3 in "Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HBV, HCV, and HIV and Recommendations for Postexposure Prophylaxis," *MMWR*, June 29, 2001, Vol. 50, RR-11.

For additional specific ACIP recommendations, refer to the official ACIP statements published in *MMWR*. To obtain copies, visit CDC's website at www.cdc.gov/vaccines/pubs/ACIP-list.htm; or visit the Immunization Action Coalition (IAC) website at www.immunize.org/acip.

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www.immunize.org/catg.d/p2017.pdf • Item #P2017 (7/08)

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Vaccination of Persons with Primary and Secondary Immune Deficiencies

PRIMARY				
Category	**Specific Immunodeficiency**	**Contraindicated Vaccines[1]**	**Risk-Specific Recommended Vaccines[1]**	**Effectiveness & Comments**
B-lymphocyte (humoral)	Severe antibody deficiencies (e.g., X-linked agammaglobulinemia and common variable immunodeficiency)	OPV[2] Smallpox LAIV BCG Ty21a (live oral typhoid) Yellow Fever	Pneumococcal Influenza (TIV) Consider measles and varicella vaccination.	The effectiveness of any vaccine will be uncertain if it depends only on the humoral response; IGIV interferes with the immune response to measles vaccine and possibly varicella vaccine.
	Less severe antibody deficiencies (e.g., selective IgA deficiency and IgG subclass deficiency	OPV[2] BCG Ty21a (live oral typhoid) Other live vaccines appear to be safe.	Pneumococcal Influenza (TIV)	All vaccines probably effective. Immune response may be attenuated.
T-lymphocyte (cell-mediated and humoral)	Complete defects (e.g., severe combined immunodeficiency [SCID] disease, complete DiGeorge syndrome)	All live vaccines [3,4]	Pneumococcal Influenza (TIV)	Vaccines may be ineffective.
	Partial defects (e.g., most patients with DiGeorge syndrome, Wiskott-Aldrich syndrome, ataxia-telangiectasia)	All live vaccines [3,4]	Pneumococcal Meningococcal Hib (if not administered in infancy) Influenza (TIV)	Effectiveness of any vaccine depends on degree of immune suppression.
Complement	Deficiency of early components (C1-C4), late components (C5-C9), properdin, factor B.	None	Pneumococcal Meningococcal Influenza (TIV)	All routine vaccines probably effective.
Phagocytic function	Chronic granulomatous disease, leukocyte adhesion defects, and myeloperoxidase deficiency.	Live bacterial vaccines[3]	Pneumococcal[5] Influenza (TIV) (to decrease secondary bacterial infection).	All inactivated vaccines safe and probably effective. Live viral vaccines probably safe and effective.

[1] Other vaccines that are not specifically contraindicated may be used if otherwise indicated.
[2] OPV is no longer licensed in the United States, and therefore is not recommended for routine use.
[3] Live bacterial vaccines: BCG, and Ty21a *Salmonella typhi* vaccine.
[4] Live viral vaccines: MMR, OPV, LAIV, yellow fever, varicella (including MMRV and zoster vaccine), and vaccinia (smallpox). Smallpox vaccine is not recommended for children or the general public.
[5] Pneumococcal vaccine is not indicated for children with chronic granulomatous disease.

Vaccination of Persons with Primary and Secondary Immune Deficiencies

SECONDARY			
Specific Immunodeficiency	**Contraindicated Vaccines[1]**	**Recommended Vaccines[1]**	**Effectiveness & Comments**
HIV/AIDS	OPV[2] Smallpox BCG LAIV Withhold MMR and varicella in severely immunocompromised persons.	Influenza (TIV) Pneumococcal Consider Hib (if not administered in infancy) and Meningococcal vaccination.	MMR, varicella, and all inactivated vaccines, including inactivated influenza, might be effective.[3]
Malignant neoplasm, transplantation, immunosuppressive or radiation therapy	Live viral and bacterial, depending on immune status.[4,5]	Influenza (TIV) Pneumococcal	Effectiveness of any vaccine depends on degree of immune suppression.
Asplenia	None	Pneumococcal Meningococcal Hib (if not administered in infancy)	All routine vaccines probably effective.
Chronic renal disease	LAIV	Pneumococcal Influenza (TIV) Hepatitis B	All routine vaccines probably effective.

[1] Other vaccines that are not specifically contraindicated may be used if otherwise indicated.
[2] OPV is no longer licensed in the United States, and therefore is not recommended for routine use.
[3] HIV-infected children should receive IG after exposure to measles, and may receive varicella and measles vaccine if CD4+ lymphocyte count is ≥15%.
[4] Live viral vaccines: MMR, OPV, LAIV, yellow fever, varicella (including MMRV and zoster vaccine), and vaccinia (smallpox). Smallpox vaccine is not recommended for children or the general public.
[5] Live bacterial vaccines: BCG, and Ty21a *Salmonella typhi* vaccine.

AIDS: Acquired Immunodeficiency Syndrome
BCG: Bacilli Calmette-Guerin vaccine
Hib: *Haemophilus influenzae* type b vaccine
HIV: Human Immunodeficiency Virus
IGIV: Immune Globulin Intravenous
IG: Immunoglobulin
LAIV: Live, Attenuated Influenza Vaccine
MMR: Measles, Mumps, Rubella vaccine
OPV: Oral Poliovirus Vaccine (live)
TIV: Trivalent (inactivated) Influenza Vaccine

Modified from American Academy of Pediatrics. Passive Immunization. In: Pickering LK, Baker C, Long S, McMillen J, ed. *Red Book: 2006 Report of the Committee on Infectious Diseases*. 27th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2006: [71-72] and CDC. General Recommendations on Immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2006: 55 (No. RR-15).

APPENDIX B
Vaccines

U.S. Vaccines **B1**

Selected Discontinued U.S. Vaccines **B6**

Vaccine Excipient and Media Summary, by Excipient **B8**

Vaccine Excipient and Media Summary, by Vaccine **B15**

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Pediatric/VFC Vaccine Price List **B21**

Adult Vaccine Price List **B23**

Influenza Vaccine Price List **B23**

Foreign Language Terms **B24**

Appendix B

U.S. Vaccines

Vaccine	Trade Name	Abbreviation	Manufacturer	Type	Route	Comments
Anthrax	BioThrax	AVA	BioPort	Inactivated Bacterial	IM	
DTaP	Daptacel	DTaP	sanofi	Inactivated Bacterial	IM	Tetanus & diphtheria toxoids and pertussis vaccine. Not licensed for 5th dose.
	Infanrix	DTaP	GlaxoSmithKline	Inactivated Bacterial	IM	Tetanus & diphtheria toxoids and pertussis vaccine.
	Tripedia	DTaP	sanofi	Inactivated Bacterial	IM	Tetanus & diphtheria toxoids and pertussis vaccine.
Diphtheria - Tetanus	(Generic)	DT	sanofi	Inactivated Bacterial Toxoids	IM	Pediatric formulation
DTaP/Hib	TriHIBit	DTaP/Hib	sanofi	Inactivated Bacterial	IM	ActHIB reconstituted with Tripedia. Licensed for 4th dose of DTaP & Hib series (not primary series).
DTaP-IPV	Kinrix	DTaP-IPV	GlaxoSmithKline	Inactivated Bacterial & Viral	IM	Licensed for 5th (DTaP) and 4th (IPV) booster at 4-6 years
DTaP-HepB-IPV	Pediarix	DTaP-HepB-IPV	GlaxoSmithKline	Inactivated Bacterial & Viral	IM	Licensed for doses at 2, 4, 6 months (through 6 years of age). Not licensed for boosters.
DTaP-IPV/Hib	Pentacel	DTaP-IPV/Hib	sanofi	Inactivated Bacterial & Viral	IM	Licensed for 4 doses at 2, 4, 6, and 15-18 months.
Haemophilus influenzae type b (Hib)	PedvaxHIB	Hib	Merck	Inactivated Bacterial	IM	**PRP-OMP**. Polysaccharide conjugate (mening. protein carrier). 2-dose schedule.
	ActHIB	Hib	sanofi	Inactivated Bacterial	IM	**PRP-T**. Polysaccharide conjugate (tetanus toxoid carrier). 3-dose schedule.
Haemophilus influenzae type b - Hepatitis B	Comvax	Hib-HepB	Merck	Inactivated Bacterial & Viral	IM	Should not be used for HepB birth dose.

Vaccine	Trade Name	Abbreviation	Manufacturer	Type	Route	Comments
Hepatitis A	Havrix	HepA	GlaxoSmithKline	Inactivated Viral	IM	Pediatric (≤18) and adult formulations. Pediatric = 720 EL.U., 0.5mL Adult = 1,140 EL.U., 1.0mL Minimum age = 1 year.
	Vaqta	HepA	Merck	Inactivated Viral	IM	Pediatric (≤18) and adult formulations. Pediatric = 25 U, 0.5mL Adult = 50 U, 1.0mL Minimum age = 1 year.
Hepatitis B	Engerix-B	HepB	GlaxoSmithKline	Inactivated Viral	IM	Pediatric (≤19) and adult formulations. Pediatric formulation is not licensed for adults.
	Recombivax HB	HepB	Merck	Inactivated Viral	IM	Pediatric (≤19), adult, and dialysis formulations. Two pediatric doses may be substituted for an adult dose.
Hepatitis A - Hepatitis B	Twinrix	HepA-HepB	GlaxoSmithKline	Inactivated Viral	IM	Pediatric dose of HepA + adult dose of HepB. Minimum age = 18 years. 3-dose series.
Herpes Zoster (Shingles)	Zostavax	ZOS	Merck	Live Viral	SC	Licensed for age 60 and older.
Human Papillomavirus (HPV)	Gardasil	HPV4	Merck	Inactivated Viral	IM	Quadrivalent, Types 6, 11, 16 & 18. Licensed for females 9-26 years.
	Cervarix	HPV2	GlaxoSmithKline	Inactivated viral	IM	Bivalent, Types 16 & 18. **NOT YET LICENSED IN U.S.**

Vaccine	Trade Name	Abbreviation	Manufacturer	Type	Route	Comments
Influenza	Fluarix	TIV	GlaxoSmithKline	Inactivated Viral	IM	Trivalent Types A & B. Minimum age = 18 years.
	Fluvirin	TIV	Chiron	Inactivated Viral	IM	Trivalent Types A & B Purified surface antigen. Minimum age = 4 years.
	Fluzone	TIV	sanofi	Inactivated Viral	IM	Trivalent Types A & B Subvirion. Minimum age multidose vial = 6 months. Age range 0.25ml prefilled syringe = 6-35 months. Minimum age 0.5ml prefilled syringe = 3 years.
	FluLaval	TIV	GlaxoSmithKline	Inactivated Viral	IM	Trivalent Types A & B Minimum age = 18 years.
	Afluria	TIV	CSL	Inactivated Viral	IM	Trivalent Types A & B Minimum age = 18 years.
	FluMist	LAIV	Medimmune	Live attenuated viral	Intra-nasal	Trivalent Types A & B. Age range 5-49 years.
Japanese Encephalitis	JE-Vax	JE	sanofi	Inactivated viral	SC	
	Ixiaro	JE	Novartis	Inactivated viral	IM	Licensed for age 17 and older.
MMR	M-M-R II	MMR	Merck	Live attenuated viral	SC	Measles, mumps, rubella.
MMRV	ProQuad	MMRV	Merck	Live attenuated viral	SC	Measles, mumps, rubella, varicella.
Meningococcal	Menomune	MPSV4	sanofi	Inactivated bacterial	SC	Polysaccharide, containing serogroups A, C, Y, & W-135.
	Menactra	MCV4	sanofi	Inactivated bacterial	IM	Polysaccharide conjugate (diphtheria toxoid carrier), containing serogroups A, C, Y, & W-135. Age range 2-49.

Vaccine	Trade Name	Abbreviation	Manufacturer	Type	Route	Comments
Pneumococcal	Pneumovax 23	PPSV23	Merck	Inactivated bacterial	SC or IM	Polysaccharide. Contains 23 strains. Minimum age = 2 yrs.
	Prevnar	PCV7	Wyeth	Inactivated bacterial, conjugate	IM	Polysaccharide conjugate (diphtheria protein carrier). Contains 7 strains. Routine age range = 2-59 months.
	PCV13	PCV13	Wyeth	Inactivated bacterial, conjugate	IM	Polysaccharide conjugate (diphtheria protein carrier). Contains 13 strains. **NOT YET LICENSED IN U.S.**
Polio	Ipol	IPV	sanofi	Inactivated viral	SC or IM	Trivalent, Types 1, 2, & 3.
Rabies	Imovax Rabies		sanofi	Inactivated viral	IM	
	RabAvert		Chiron	Inactivated viral	IM	
Rotavirus	RotaTeq	RV5	Merck	Live viral	Oral	Pentavalent. First dose between 6 weeks and 14 weeks 6 days; complete 3-dose series by 8 months 0 days.
	Rotarix	RV1	GlaxoSmithKline	Live viral	Oral	Monovalent. First dose between 6 weeks and 14 weeks 6 days; complete 2-dose series by 8 months 0 days.
Tetanus - (reduced) diphtheria	Decavac	Td	sanofi	Inactivated bacterial toxoids	IM	Tetanus/diphtheria toxoids. Adult formulation
	(Generic)	Td	Massachusetts Biological Labs	Inactivated bacterial toxoids	IM	Tetanus/diphtheria toxoids. Adult formulation
Tdap	Boostrix	Tdap	GlaxoSmithKline	Inactivated bacterial	IM	Tetanus & diphtheria toxoids & pertussis vaccine. Licensed for ages 10-64.
	Adacel	Tdap	sanofi	Inactivated bacterial	IM	Tetanus & diphtheria toxoids & pertussis vaccine. Licensed for ages 11-64.

Vaccine	Trade Name	Abbreviation	Manufacturer	Type	Route	Comments
Tetanus Toxoid	(Generic)	TT	sanofi	Inactivated bacterial toxoid	IM	Tetanus toxoid. May be used for adults or children.
Typhoid	Typhim Vi		sanofi	Inactivated bacterial	IM	Polysaccharide.
	Vivotif Berna		Berna	Live bacterial	Oral	Ty21a strain.
Varicella	Varivax	VAR	Merck	Live viral	SC	
Vaccinia (Smallpox)	ACAM2000		Acambis	Live Viral	Percu-taneous	
Yellow Fever	YF-Vax	YF	sanofi	Live viral	SC	
Zoster	(See Herpes Zoster)					

April 2009

Appendix B

Selected *Discontinued* U.S. Vaccines

Trade Name	Antigen(s)	Years
Acel-Imune	DTaP	1991-2001
Attenuvax-Smallpox	Measles-Smallpox	1967
b-CAPSA-1	Hib (polysaccharide)	1985-89
Biavax	Rubella-Mumps (live)	
BioRab	Rabies	1988-2007
Cendevax	Rubella (live)	1969-79
Certiva	DTaP	1998-2000
Dip-Pert-Tet	DTP	
Diptussis	Diphtheria/Pertussis	1949-55
Dryvax	Vaccinia	1944-2008
Ecolarix	Measles-Rubella (live)	
Flu Shield	Influenza	
Fluogen	Influenza	
Heptavax-B	Hepatitis B (plasma derived)	1981-90
HIB-Immune	Hib (polysaccharide)	1985-89
HibTITER	Hib (conjugate)	1990-2007
HIB-Vax	Hib (polysaccharide)	1985-89
Liovax	Smallpox	
Lirubel	Measles-Rubella (live)	1974-78
Lirugen	Measles (live)	1965-76
Lymerix	Lyme disease	1998-2002
M-Vac	Measles	1963-79
M-M-Vax	Measles-Mumps (live)	1973
Meningovax	Meningococcal	
Mevilin-L	Measles (live)	
MOPV	Polio (live, oral -monovalent, types I, II, & III)	
Mumpsvax	Mumps (live)	

Trade Name	Antigen(s)	Years
OmniHIB	Hib (conjugate)	
Orimune	Polio (live, oral)	1961-2000
Perdipigen	Diphtheria/Pertussis	1949-55
Pfizer-Vax Measles-K	Measles (inactivated)	1963-68
Pfizer-Vax Measles-L	Measles (live)	1965-70
Pnu-Imune	Pneumococcal (polysaccharide 14- or 23-valent)	1977-83
Poliovax	Polio (inactivated)	1988-91
ProHIBIT	Hib (conjugate)	1987-2000
Purivax	Polio (inactivated)	1956-65
Quadrigen	DTP-Polio	1959-68
Rabies Iradogen	Rabies	1908-57
RotaShield	Rotavirus	1998-99
Rubelogen	Rubella (live)	1969-72
Rubeovax	Measles (live)	1963-71
Serobacterin	Pertussis	1945-54
Solgen	DTP	1962-77
Tetra-Solgen	DTP-Polio	1959-68
Tetramune	DTP-Hib	
Tetravax	DTP-Polio	1959-65
Topagen	Pertussis (intranasal)	
Tri-Immunol	DTP	
Tridipigen	DTP	
Trinfagen No. 1	DT-Polio	Early 1960s
Trinivac	DTP	1952-64
Trivivac	DTP	
Wyvac	Rabies	1982-85

February 2008

Appendix B

Vaccine Excipient & Media Summary

This section begins with a summary of the excipients included in licensed vaccines in the United States, as of the revision date at the bottom of the page.

Excipients are inactive ingredients of a drug product necessary for production of a finished pharmaceutical formulation.

After the list of excipients is a list of culture media used in the manufacturing process of vaccines licensed in the United States.

Growth media are culture materials used to produce mass quantities of a microorganism antibody, or other immunologic agent, suitable for further processing into a finished pharmaceutical product.

All reasonable efforts have been made to ensure the accuracy of this information, but manufacturers may change product contents before that information is reflected here.

Excipients Included in US Licensed Vaccines[a]

Excipient	Use	Vaccine
Albumin, egg (Ovalbumin)	Growth medium	Influenza (*Fluarix*, *FluLaval*), Rabies (*RabAvert*)
Albumin, human serum	Component of growth medium, protein stabilizer	Measles (*Attenuvax*), MMR (*MMR-II*), MMRV (*ProQuad*), Mumps (*Mumpsvax*), Rabies (*Imovax*), Rubella (*Meruvax II*)
Albumin or serum, bovine	Component of growth medium, protein stabilizer	Hepatitis A (*Havrix, Vaqta*), Measles (*Attenuvax*), MMR (*MMR-II*), MMRV (*ProQuad*), Mumps (*Mumpsvax*), Rabies (*Imovax*, *RabAvert*), Rotavirus (*RotaTeq*), Rubella (*Meruvax II*), Vaccinia (*Dryvax*), Varicella (*Varivax*)
Aluminum hydroxide	Adjuvant	Anthrax (*BioThrax*), DTaP (*Infanrix*), DTaP-Hep B-IPV (*Pediarix*), Td (Massachusetts), Hepatitis A (*Havrix*), Hepatitis A-Hepatitis B (*Twinrix*), Hepatitis B (*Engerix-B*), Tdap (*Boostrix*)
Aluminum hydroxyphosphate sulfate	Adjuvant	Hib (*PedvaxHIB*, Hib-Hepatitis B (*Comvax*), Hepatitis A (*Vaqta*), Hepatitis B (*Recombivax HB*), Human papillomavirus (*Gardasil*)
Aluminum phosphate	Adjuvant	DTaP (*Daptacel*), Hepatitis A-Hepatitis B (*Twinrix*), Pneumococcal (*Prevnar*), Rabies (*BioRab*), Td (*Decavac*), Td (Massachusetts), Tdap (*Adacel*)
Aluminum potassium sulfate	Adjuvant	DTaP (*Daptacel*, *Tripedia*), DTaP-Hib (*TriHIBit*), DT (Sanofi Pasteur)
Amino acids	Component of growth medium	Anthrax (*BioThrax*), Hepatitis A (*Havrix*), Hepatitis A-Hepatitis B (*Twinrix*), Rotavirus (*Rotarix*), Td (Aventis Pasteur), Typhoid oral (*Vivotif*)
Ammonium sulfate	Protein fractionation	DTaP-Hib (*TriHIBit*), Hib (*Act-HIB*)
Amphotericin B	Antibacterial	Rabies (*RabAvert*)
Ascorbic acid	Antioxidant	Typhoid oral (*Vivotif*)

Vaccine Excipient & Media Summary

Excipients Included in US Licensed Vaccines[a]		
Excipient	Use	Vaccine
Bactopeptone	Component of growth medium	Influenza (varies seasonally)
Beta-propiolactone	Viral inactivator	Influenza (*Fluvirin*), Rabies (*Imovax, RabAvert*)
Benzethonium chloride	Preservative	Anthrax (*BioThrax*)
Brilliant green	Dye	Vaccinia (*Dryvax-historic*)
Calcium carbonate	Antacid	Rotavirus (*Rotarix*)
Calcium chloride	Medium nutrient	Rotavirus (*Rotarix*)
Chlortetracycline	Antibacterial	Rabies (*RabAvert*), Vaccinia (*Dryvax*)
Cystine	Medium nutrient	Rotavirus (*Rotarix*)
Dextran	Medium nutrient	Rotavirus (*Rotarix*)
DNA	Manufacturing residue	Hepatitis A (*Vaqta*)
Dulbecco's Modified Eagle Medium (DMEM)	Growth medium	Rotavirus (*Rotarix*)
Ethylenediamine-tetraacetic acid sodium (EDTA)	Preservative	Rabies (*RabAvert*), Varicella (*Varivax*)
Egg protein	Manufacturing residue	Influenza (all brands), Yellow fever (*YF-Vax*)
Ferric (III) nitrate	Medium nutrient	Rotavirus (*Rotarix*)
Formaldehyde, formalin	Antimicrobial, toxin inactivator, stabilizier	Anthrax (*BioThrax*), DTaP (all brands), DTaP-Hep B-IPV (*Pediarix*), DTaP-Hib (*TriHIBit*), DT (all brands), Td (all brands), Hepatitis A (*Havrix, Vaqta*), Hepatitis A-Hepatitis B (*Twinrix*), Hib (*ActHIB*), Hib-Hepatitis B (*Comvax*), Influenza (*Fluzone, Fluarix, FluLaval*), Japanese encephalitis (*JE-Vax*), Poliovirus inactivated (*Ipol*), Tdap (*Adacel, Boostrix*)
Gelatin	Stabilizer in freeze-drying, solvent	DTaP (*Tripedia*), DTaP-Hib (*TriHIBit*), Hepatitis B (*Recombivax-HB*), Human papillomavirus (*Gardasil*), Influenza (*Fluzone*), Japanese encephalitis (*JE-Vax*), Measles (*Attenuvax*), Mumps (*Mumpsvax*), Rubella (*Meruvax II*), MMR (*MMR-II*), MMRV (*ProQuad*), Rabies (*RabAvert*), Typhoid oral (*Vivotif*), Varicella (*Varivax*), Yellow fever (*YF-Vax*), Zoster (*Zostavax*)
Gentamicin	Antibacterial	Influenza (*Fluarix, FluMist*)
Glucose	Medium nutrient	Rotavirus (*Rotarix*)
Glutamine	Medium nutrient	Rotavirus (*Rotarix*)
Glutaraldehyde	Toxin detoxifier	DTaP (*Infanrix*), DTaP-Hep B-IPV (*Pediarix*), Tdap (*Boostrix*)
Glycerin	Solvent	Vaccinia (*DryVax*)
Glycine	Protein stabilizer	DT (most brands), Td (most brands)
Histidine	Stabilizer	Human papillomavirus (*Gardasil*)
Hydrochloric acid	Adjust pH	DTaP (most brands), DT (most brands)

Vaccine Excipient & Media Summary

Excipients Included in US Licensed Vaccines[a]		
Excipient	Use	Vaccine
Hydrocortisone	Component of growth medium	Influenza (*Fluarix*)
Lactose	Stabilizer in freeze-drying, filling	BCG (*Tice*), Hib (some packages), Meningococcal (*Menomune*), Typhoid oral (*Vivotif*)
Magnesium stearate	Lubricant for capsule filling	Typhoid oral (*Vivotif*)
Magnesium sulfate	Medium nutrient	Rotavirus (*Rotarix*)
Monosodium glutamate	Stabilizer	Influenza (*FluMist*), MMRV (*ProQuad*), Varicella (*Varivax*), Zoster (*Zostavax*)
Mouse serum protein	Manufacturing residue	Japanese encephalitis (*JE-Vax*)
MRC-5 cellular protein	Manufacturing residue	Hepatitis A (*Havrix*, *Vaqta*), Hepatitis A-Hepatitis B (*Twinrix*), MMRV (*ProQuad*), Rabies (*Imovax*), Poliovirus inactivated (*Poliovax*), Varicella (*Varivax*)
Neomycin	Antibacterial	DTaP-Hep B-IPV (*Pediarix*), Hepatitis A-Hepatitis B (*Twinrix*), Influenza (*Fluvirin*), Measles (*Attenuvax*), Mumps (*Mumpsvax*), Rubella (*Meruvax II*), MMR (*MMR-II*), MMRV (*ProQuad*), Poliovirus inactivated (*Ipol*), Rabies (*Imovax*, *RabAvert*), Vaccinia (*DryVax*), Varicella (*Varivax*), Zoster (*Zostavax*)
Phenol	Preservative, antibacterial	Pneumococcal (*Pneumovax-23*), Typhoid inactivated (*Typhim Vi*), Vaccinia (*Dryvax*)
Phenol red (phenolsulfonphthalein)	pH indicator, dye	Rabies (*Imovax*), Rotavirus (*Rotarix*)
2-Phenoxyethanol	Preservative, stabilizer	DTaP (*Infanrix*, *Daptacel*), DTaP-Heb B-IPV (*Pediarix*), Hepatitis A (*Havrix*), Hepatitis A-Hepatitis B (*Twinrix*), Poliovirus inactivated (*Ipol*), Td (Sanofi Pasteur)
Phosphate buffers (eg, disodium, monosodium, potassium, sodium dihydrogenphosphate)	Adjust pH	DTaP (most brands), DT (most brands), Hib (*Act-Hib*), Hepatitis A (*Havrix*), Hepatitis A-Hepatitis B (*Twinrix*), Hepatitis B (*Engerix-B*), Influenza (*Fluarix*, *FluMist*, *FluLaval*), Measles (*Attenuvax*), Meningococcal (*Menactra*), Mumps (*Mumpsvax*), Poliovirus inactivated (*Ipol*), Rabies (*BioRab*), Rubella (*Meruvax II*), MMR (*MMR-II*), MMRV (*ProQuad*), Rotavirus (*RotaTeq*), Typhoid inactivated (*Typhim Vi*), Varicella (*Varivax*), Zoster (*Zostavax*)
Polydimethylsilozone	Antifoaming agent	Typhoid inactivated (*Typhim Vi*)
Polymyxin B	Antibacterial	DTaP-Heb B-IPV (*Pediarix*), Influenza (*Fluvirin*), Poliovirus inactivated (*Ipol*), Vaccinia (*Dryvax*)

Vaccine Excipient & Media Summary

Excipients Included in US Licensed Vaccines[a]		
Excipient	Use	Vaccine
Polyoxyethylene9-10 nonyl phenol (Triton N-101, octoxynol 9)	Nonionic surfactant (viral inactivation)	Influenza (*Fluvirin*)
Polyoxyethylated octyl phenol (also called ethylene glycol octyl phenyl ether, octoxynol-10, octyl-phenoxypolyethoxyethanol, p-isooctyphenyl ether, Triton X-100)	Nonionic surfactant (viral inactivation)	Influenza (*Fluarix*, *Fluzone*)
Polysorbate 20	Surfactant	Hepatitis A (*Havrix*), Hepatitis A-Hepatitis B (*Twinrix*)
Polysorbate 80	Surfactant	DTaP (*Infanrix*, *Tripedia*), DTaP-Heb B-IPV (*Pediarix*), DTaP-Hib (*TriHIBit*), Human papillomavirus (*Gardasil*), Influenza (*Fluarix*), Rotavirus (*RotaTeq*), Tdap (*Adacel*, *Boostrix*)
Potassium chloride	Adjust pH, tonicity, medium nutrient	MMRV (*ProQuad*), Rotavirus (*Rotarix*), Zoster (*Zostavax*)
Potassium glutamate	Stabilizer	Rabies (*RabAvert*)
Serum, bovine calf	Component of growth medium	Zoster (*Zostavax*)
Sodium acetate	Adjust pH	DT (some brands), Td (some brands)
Sodium bicarbonate	Adjust pH	MMRV (*ProQuad*)
Sodium borate	Adjust pH	Hepatitis A (*Vaqta*), Hib-Hepatitis B (*Comvax*), Human papillomavirus (*Gardasil*)
Sodium chloride	Adjust tonicity	Most vaccines, including Anthrax, BCG, Human papillomavirus (*Gardasil*), Influenza (*Fluarix*), Measles, Meningococcal (*Menactra*), Mumps, MMR, MMRV, Pneumococcal, Polio inactivated, Rabies, Rotavirus (*Rotarix*), Rubella, Typhoid inactivated, Varicella, Yellow fever, Tdap (*Boostrix*), Zoster (*Zostavax*)
Sodium citrate	Adjust pH	Rotavirus (*RotaTeq*)
Sodium deoxycholate	Anionic surfactant (viral inactivation)	Influenza (*Fluarix*, *FluLaval*)
Sodium hydrogenocarbonate	Medium nutrient	Rotavirus (*Rotarix*)
Sodium hydroxide	Adjust pH	DT (most brands), Rotavirus (*RotaTeq*), Td (most brands)
Sodium phosphate	Medium nutrient	Rotavirus (*Rotarix*)
Sodium pyruvate	Medium nutrient	Rotavirus (*Rotarix*)
Sorbitol	Stabilizer, solvent	Measles (*Attenuvax*), Mumps (*Mumpsvax*), Rotavirus (*Rotarix*), Rubella (*Meruvax II*), MMR (*MMR-II*), MMRV (*ProQuad*), Yellow fever (*YF-Vax*)
Streptomycin	Antibacterial	Poliovirus inactivated (*Ipol*), Vaccinia (*Dryvax*)

Appendix B

Vaccine Excipient & Media Summary

Excipients Included in US Licensed Vaccines[a]		
Excipient	Use	Vaccine
Sucrose	Stabilizer	DTaP-Hib (*TriHIBit*), Hib (*Act-HIB*), Influenza (*FluMist*), Measles (*Attenuvax*), Mumps (*Mumpsvax*), MMR (*MMR-II*), MMRV (*ProQuad*), Rotavirus (*RotaTeq*), Typhoid oral (*Vivotif*), Varicella (*Varivax*), Zoster (*Zostavax*)
Sucrose	Medium nutrient	Rotavirus (*Rotarix*)
Thimerosal	Preservative in some multidose containers (see package labeling for precise content)	DTaP (some multidose containers), DTaP-Hib (*TriHIBit*), DT (some multidose containers), Td (some multidose containers), Hib (some multidose containers), Influenza (some multidose containers), Japanese encephalitis (*JE-Vax*), Meningococcal (*Menomune*), Rabies (*BioRab*). Some single-dose containers contain trace amounts of thimerosal from the production process, but substantially lower concentrations than if used as a preservative. Consult product monographs and labeling for details.
Tocopheryl hydrogen succinate	Component of growth medium	Influenza (*Fluarix*)
Tyrosine	Medium nutrient	Rotavirus (*Rotarix*)
Urea	Stabilizer	Varicella vaccine (*Varivax*, refrigerator stable)
Vitamins unspecified	Component of growth medium	Anthrax (*BioThrax*), Rabies (*Imovax*), Rotavirus (*Rotarix*), Td (Sanofi Pasteur)
Xanthan	Thickening agent	Rotavirus (*Rotarix*)
Yeast protein	Component of growth medium	DTaP-Heb B-IPV (*Pediarix*), Hepatitis A-Hepatitis B (*Twinrix*), Hepatitis B (*Engerix-B*, *Recombivax-HB*), Hib (*HibTiter*), Hib-Hepatitis B (*Comvax*)

a Proprietary names appear in italics.

Vaccine Excipient & Media Summary

Vaccine-Production Media[a]	
Vaccine Culture Media	Vaccine(s)
Bovine protein	DTaP-Hep B-IPV (poliovirus component, *Pediarix*), Pneumococcal (*Pneumovax-23*), Typhoid oral (*Vivotif*)
Calf skin	Vaccinia (*Dryvax*)
Chick embryo fibroblast tissue culture	Measles (*Attenuvax*), Mumps (*Mumpsvax*), combination vaccines containing them, MMRV (*ProQuad*), Rabies (*RabAvert*)
Chick kidney cells	Influenza (master viruses for *FluMist*)
Chicken embryo (fertilized egg)	Influenza (all brands), Yellow fever (*YF-Vax*)
Cohen-Wheeler, modified (pertussis components)	DTaP (alternate is Stainer-Scholte media)
Fenton media containing bovine casein	Tdap (*Boostrix*)
Human diploid tissue culture, MRC-5	Hepatitis A (*Havrix*, *Vaqta*), Hepatitis A-Hepatitis B (*Twinrix*), MMRV (*ProQuad*), Poliovirus inactivated (*Poliovax*), Rabies (*Imovax*), Varicella (*Varivax*), Zoster (*Zostavax*)
Human diploid tissue culture, WI-38	Rubella (*Meruvax II*), combination vaccines containing it, MMRV (*ProQuad*), Varicella (*Varivax*), Zoster (*Zostavax*)
Lathan medium derived from bovine casein	DTaP (*Infanrix*, tetanus component), DTaP-Hep B-IPV (*Pediarix*), Tdap (*Boostrix*)
Linggoud-Fenton medium containing bovine extract	DTaP (*Infanrix* diphtheria component), DTaP-Hep B-IPV (*Pediarix*), Tdap (*Boostrix*)
Medium 199 (including amino acids, vitamins, sucrose, phosphate, glutamate, human albumin, fetal bovine serum)	Measles (*Attenuvax*), Mumps (*Mumpsvax*), combination vaccines containing them
Minimum essential medium (including amino acids, vitamins, fetal bovine serum, human albumin)	Rubella (*Meruvax II*), combination vaccines containing it
Monkey kidney tissue culture, Vero (Vervet or African green monkeys)	DTaP-Hep B-IPV (poliovirus component, *Pediarix*), Poliovirus inactivated (*Ipol*), Rotavirus (*RotaTeq*)
Mouse brain culture	Japanese encephalitis (*JE-Vax*)
Mueller-Hinton agar medium	Meningococcal conjugate (*Menactra*)
Mueller-Miller medium	Diphtheria and tetanus vaccines (most brands), meningococcal conjugate (*Menactra*)
Puziss-Wright medium 1095	Anthrax (*BioThrax*)
Rhesus fetal lung tissue culture	Rabies (*BioRab*)
Stainer-Scholte medium	DTaP (*Daptacel*, *Infanrix*, pertussis component), DTaP-Hep B-IPV (*Pediarix*), Tdap (*Boostrix*)
Soy peptone broth	Pneumococcal (*Prevnar*)
Synthetic/semi-synthetic	Anthrax (*BioThrax*), BCG (*Tice*), DT (all brands), Td (all brands), Hib (all brands), Meningococcal (*Menomune*), Pneumococcal (*Pneumovax-23*), Typhoid inactivated (*Typhim Vi*)
Watson-Scherp medium	Meningococcal conjugate (*Menactra*)
Yeast or yeast extract (typically *Saccharomyces cerevisiae*)	Hepatitis A-Hepatitis B (*Twinrix*), Hepatitis B (*Engerix-B*, *Recombivax-HB*), Hib (*HibTiter*, *PedvaxHIB*), Hib-Hepatitis B (*Comvax*), Human papillomavirus (*Gardasil*), Medium for growing *Corynebacterium diphtheriae* strain C7 (b197) to obtain CRM_{197} protein for conjugation to polysaccharides (*HibTiter*, *Prevnar*).

a Proprietary names appear in italics.

References: Canadian National Advisory Committee on Immunization. Statement on thimerosal. *Can Comm Dis Rep*. 2003;29(ACS-1):1-10.

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Reprinted courtesy of Grabenstein JD. *ImmunoFacts: Vaccines & Immunologic Drugs*. St. Louis, MO: Wolters Kluwer Health, Inc.; 2009.

Vaccine Excipient & Media Summary, Part 2

Excipients Included in U.S. Vaccines, by Vaccine

Includes vaccine ingredients (e.g., adjuvants and preservatives) as well as substances used during the manufacturing process, including vaccine-production media, that are removed from the final product and present only in trace quantities. In addition to the substances listed, most vaccines contain Sodium Chloride (table salt).

Vaccine	Contains
Anthrax (BioThrax)	Aluminum Hydroxide, Amino Acids, Benzethonium Chloride, Formaldehyde or Formalin, Inorganic Salts and Sugars, Vitamins
BCG (Tice)	Asparagine, Citric Acid, Lactose, Glycerin, Iron Ammonium Citrate, Magnesium Sulfate, Potassium Phosphate
DTaP (Daptacel)	Aluminum Phosphate, Ammonium Sulfate, Casamino Acid, Dimethyl-beta-cyclodextrin, Formaldehyde or Formalin, Glutaraldehyde, 2-Phenoxyethanol
DTaP (Infanrix)	Aluminum Hydroxide, Bovine Extract, Formaldehyde or Formalin, Glutaraldhyde, 2-Phenoxyethanol, Polysorbate 80
DTaP (Tripedia)	Aluminum Potassium Sulfate, Ammonium Sulfate, Bovine Extract, Formaldehyde or Formalin, Gelatin, Polysorbate 80, Sodium Phosphate, Thimerosal*
DTaP/Hib (TriHIBit)	Aluminum Potassium Sulfate, Ammonium Sulfate, Bovine Extract, Formaldehyde or Formalin, Gelatin, Polysorbate 80, Sucrose, Thimerosal*
DTaP-IPV (Kinrix)	Aluminum Hydroxide, Bovine Extract, Formaldehyde, Lactalbumin Hydrolysate, Monkey Kidney Tissue, Neomycin Sulfate, Polymyxin B, Polysorbate 80
DTaP-HepB-IPV (Pediarix)	Aluminum Hydroxide, Aluminum Phosphate, Bovine Protein, Lactalbumin Hydrolysate, Formaldehyde or Formalin, Glutaraldhyde, Monkey Kidney Tissue, Neomycin, 2-Phenoxyethanol, Polymyxin B, Polysorbate 80, Yeast Protein
DtaP-IPV/Hib (Pentacel)	Aluminum Phosphate, Bovine Serum Albumin, Formaldehyde, Glutaraldhyde, MRC-5 DNA and Cellular Protein, Neomycin, Polymyxin B Sulfate, Polysorbate 80, 2-Phenoxyethanol,
DT (sanofi)	Aluminum Potassium Sulfate, Bovine Extract, Formaldehyde or Formalin, Thimerosal (multi-dose) or Thimerosal* (single-dose)
DT (Massachusetts)	Aluminum Hydroxide, Formaldehyde or Formalin
Hib (ACTHib)	Ammonium Sulfate, Formaldehyde or Formalin, Sucrose
Hib (PedvaxHib)	Aluminum Hydroxyphosphate Sulfate
Hib/Hep B (Comvax)	Amino Acids, Aluminum Hydroxyphosphate Sulfate, Dextrose, Formaldehyde or Formalin, Mineral Salts, Sodium Borate, Soy Peptone, Yeast Protein
Hep A (Havrix)	Aluminum Hydroxide, Amino Acids, Formaldehyde or Formalin, MRC-5 Cellular Protein, Neomycin Sulfate, 2-Phenoxyethanol, Phosphate Buffers, Polysorbate
Hep A (Vaqta)	Aluminum Hydroxyphosphate Sulfate, Bovine Albumin or Serum, DNA, Formaldehyde or Formalin, MRC-5 Cellular Protein, Sodium Borate
Hep B (Engerix-B)	Aluminum Hydroxide, Phosphate Buffers, Thimerosal*, Yeast Protein

Appendix B

Vaccine	Contains
Hep B (Recombivax)	Aluminum Hydroxyphosphate Sulfate, Amino Acids, Dextrose, Formaldehyde or Formalin, Mineral Salts, Potassium Aluminum Sulfate, Soy Peptone, Yeast Protein
HepA/HepB (Twinrix)	Aluminum Hydroxide, Aluminum Phosphate, Amino Acids, Dextrose, Formaldehyde or Formalin, Inorganic Salts, MRC-5 Cellular Protein, Neomycin Sulfate, 2-Phenoxyethanol, Phosphate Buffers, Polysorbate 20, Thimerosal*, Vitamins, Yeast Protein
Human Papillomavirus (HPV) (Gardasil)	Amino Acids, Amorphous Aluminum Hydroxyphosphate Sulfate, Carbohydrates, L-histidine, Mineral Salts, Polysorbate 80, Sodium Borate, Vitamins
Influenza (Afluria)	Beta-Propiolactone, Calcium Chloride, Neomycin, Ovalbumin, Polymyxin B, Potassium Chloride, Potassium Phosphate, Sodium Phosphate, Sodium Taurodeoxychoalate.
Influenza (Fluarix)	Egg Albumin (Ovalbumin), Egg Protein, Formaldehyde or Formalin, Gentamicin, Hydrocortisone, Octoxynol-10, α-Tocopheryl Hydrogen Succinate, Polysorbate 80, Sodium Deoxycholate, Sodium Phosphate, Thimerosal*
Influenza (Flulaval)	Egg Albumin (Ovalbumin), Egg Protein, Formaldehyde or Formalin, Sodium Deoxycholate, Phosphate Buffers, Thimerosal
Influenza (Fluvirin)	Beta-Propiolactone , Egg Protein, Neomycin, Polymyxin B, Polyoxyethylene 9-10 Nonyl Phenol (Triton N-101, Octoxynol 9), Thimerosal (multidose containers), Thimerosal* (single-dose syringes)
Influenza (Fluzone)	Egg Protein, Formaldehyde or Formalin, Gelatin, Octoxinol-9 (Triton X-100), Thimerosal (multidose containers)
Influenza (FluMist)	Chick Kidney Cells, Egg Protein, Gentamicin Sulfate, Monosodium Glutamate, Sucrose Phosphate Glutamate Buffer
IPV (Ipol)	Calf Serum Protein, Formaldehyde or Formalin, Monkey Kidney Tissue, Neomycin, 2-Phenoxyethanol, Polymyxin B, Streptomycin,
Japanese Encephalitis (JE-Vax)	Formaldehyde or Formalin, Gelatin, Mouse Serum Protein, Polysorbate 80, Thimerosal
Japanese Encephalitis (Ixiaro)	Aluminum Hydroxide, Bovine Serum Albumin, Formaldehyde, Protamine Sulfate, Sodium Metabisulphite
Meningococcal (Menactra)	Formaldehyde or Formalin, Phosphate Buffers
Meningococcal (Menomune)	Lactose, Thimerosal (10-dose vials only)
MMR (MMR-II)	Amino Acid, Bovine Albumin or Serum, Chick Embryo Fibroblasts, Human Serum Albumin, Gelatin, Glutamate, Neomycin, Phosphate Buffers, Sorbitol, Sucrose, Vitamins
MMRV (ProQuad)	Bovine Albumin or Serum, Gelatin, Human Serum Albumin, Monosodium L-glutamate, MRC-5 Cellular Protein, Neomycin, Sodium Phosphate Dibasic, Sodium Bicarbonate, Sorbitol, Sucrose, Potassium Phosphate Monobasic, Potassium Chloride, Potassium Phosphate Dibasic
Pneumococcal (Pneumovax)	Bovine Protein, Phenol
Pneumococcal (Prevnar)	Aluminum Phosphate, Amino Acid, Soy Peptone, Yeast Extract

Vaccine	Contains
Rabies (Imovax)	Human Serum Albumin, Beta-Propiolactone, MRC-5 Cellular Protein, Neomycin, Phenol Red (Phenolsulfonphthalein), Vitamins
Rabies (RabAvert)	Amphotericin B, Beta-Propiolactone, Bovine Albumin or Serum, Chicken Protein, Chlortetracycline, Egg Albumin (Ovalbumin), Ethylenediamine-Tetraacetic Acid Sodium (EDTA), Neomycin, Potassium Glutamate
Rotavirus (RotaTeq)	Cell Culture Media, Fetal Bovine Serum, Sodium Citrate, Sodium Phosphate Monobasic Monohydrate, Sodium Hydroxide Sucrose, Polysorbate 80
Rotavirus (Rotarix)	Amino Acids, Calcium Carbonate, Calcium Chloride, D-glucose, Dextran, Ferric (III) Nitrate, L-cystine, L-tyrosine, Magnesium Sulfate, Phenol Red, Potassium Chloride, Sodium Hydrogenocarbonate, Sodium Phosphate, Sodium L-glutamine, Sodium Pyruvate, Sorbitol, Sucrose, Vitamins, Xanthan
Td (Decavac)	Aluminum Potassium Sulfate, Bovine Extract, Formaldehyde or Formalin, 2-Phenoxyethanol, Peptone, Thimerosal*
Td (Massachusetts)	Aluminum Hydroxide, Aluminum Phosphate, Formaldehyde or Formalin, Thimerosal (some multidose containers)
Tdap (Adacel)	Aluminum Phosphate, Formaldehyde or Formalin, Glutaraldehyde, 2-Phenoxyethanol
Tdap (Boostrix)	Aluminum Hydroxide, Bovine Extract, Formaldehyde or Formalin, Glutaraldehyde, Polysorbate 80
Typhoid (inactivated – Typhim Vi)	Disodium Phosphate, Monosodium Phosphate, Phenol, Polydimethylsilozone, Hexadecyltrimethylammonium Bromide
Typhoid (oral – Ty21a)	Amino Acids, Ascorbic Acid, Bovine Protein, Casein, Dextrose, Galactose, Gelatin, Lactose, Magnesium Stearate, Sucrose, Yeast Extract
Vaccinia (ACAM2000)	Glycerin, Human Serum Albumin, Mannitol, Monkey Kidney Cells, Neomycin, Phenol, Polymyxin B
Varicella (Varivax)	Bovine Albumin or Serum, Ethylenediamine-Tetraacetic Acid Sodium (EDTA), Gelatin, Monosodium L-Glutamate, MRC-5 DNA and Cellular Protein, Neomycin, Potassium Chloride, Potassium Phosphate Monobasic, Sodium Phosphate Monobasic, Sucrose
Yellow Fever (YF-Vax)	Egg Protein, Gelatin, Sorbitol
Zoster (Zostavax)	Bovine Calf Serum, Hydrolyzed Porcine Gelatin, Monosodium L-glutamate, MRC-5 DNA and Cellular Protein, Neomycin, Potassium Phosphate Monobasic, Potassium Chloride, Sodium Phosphate Dibasic, Sucrose

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*Where "thimerosal" is marked with an asterisk (*) it indicates that the product should be considered equivalent to thimerosal-free products. This vaccine may contain trace amounts (<0.3 mcg) of mercury left after post-production thimerosal removal, but these amounts have no biological effect. *JAMA* 1999;282(18) and *JAMA* 2000;283(16)

Adapted from Grabenstein JD. *ImmunoFacts: Vaccines & Immunologic Drugs*. St. Louis, MO: Wolters Kluwer Health Inc.; 2009 and individual products' package inserts.

All reasonable efforts have been made to ensure the accuracy of this information, but manufacturers may change product contents before that information is reflected here.

Appendix B

Latex in Vaccine Packaging

"If a person reports a severe (anaphylactic) allergy to latex, vaccines supplied in vials or syringes that contain natural rubber should not be administered unless the benefit of vaccination outweighs the risk for a potential allergic reaction. For latex allergies other than anaphylactic allergies (e.g., a history of contact allergy to latex gloves), vaccines supplied in vials or syringes that contain dry natural rubber or rubber latex can be administered." (ACIP *General Recommendations on Immunization*. 2006)

The following table is accurate, to the best of our knowledge, as of April 2009. If in doubt, check the package insert for the vaccine in question.

Vaccine		Latex?
Anthrax (BioThrax)		YES – Vial.
Comvax		YES – Vial
DTaP	Daptacel	YES – Vial
	Infanrix	YES – Syringe NO – Vial
	Tripedia	YES – Vial
DT (Generic)		YES – Vial
Hib	HibTITER	YES – Vial
	PedvaxHIB	Yes – Vial
	ActHIB	YES – Diluent vial NO – Lyophilized vaccine vial
Hepatitis A	Havrix	YES – Syringe NO – Vial
	Vaqta	YES – Vial YES – Syringe
Hepatitis B	Engerix-B	YES – Syringe NO – Vial
	Recombivax HB	YES – Vial
HPV (Gardasil)		NO
Influenza	Fluarix	YES – Syringe
	Fluvirin	NO
	Fluzone	NO
	FluLaval	NO
	Afluria	NO
	FluMist	NO
Japanese Encephalitis	JE-Vax	NO
	Ixiaro	NO
Kinrix		YES – Syringe NO – Vial
MMR (M-M-R II)		NO
MMRV (ProQuad)		NO
Measles (Attenuvax)		NO
Mumps (Mumpsvax)		NO
Rubella (Meruvax II)		NO
Meningococcal	Menomune	YES – Vial
	Menactra	YES – Vial NO – Syringe

Vaccine		Latex?
Pediarix		YES – Syringe NO – Vial
Pentacel		NO
Pneumococcal	Pneumovax 23	NO
	Prevnar	YES – Vial
Polio (IPOL)		YES – Syringe NO – Vial
Rabies	Imovax Rabies	NO
	RabAvert	NO
Rotavirus	RotaTeq	NO
	Rotarix	YES – Applicator NO – Vial & Transfer Adapter
Td	Decavac	NO – Vial NO – Syringe
	Generic	YES – Vial YES – Syringe
Tdap	Adacel	NO
	Boostrix	YES – Syringe NO – Vial
TriHIBit		YES – Vial
Twinrix		YES – Syringe NO – Vial
Typhoid	Typhim Vi	NO
	Vivotif Berna	N/A
Varicella (Varivax)		NO
Vaccinia (Smallpox) (ACAM2000)		NO
Yellow Fever (YF-Vax)		YES – Vial

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Appendix B

Institute for Vaccine Safety **THIMEROSAL TABLE** (updated 8/6/08) www.vaccinesafety.edu

Vaccine	Brand Name		Manufacturer	Thimerosal Concentration[1]	Mercury mcg/0.5 ml
Anthrax	BioThrax		BioPort Corporation	**0**	**0**
DTaP	Tripedia		sanofi pasteur	*	*
	Infanrix		GlaxoSmithKline	**0**	**0**
	DAPTACEL		sanofi pasteur	**0**	**0**
DTaP-HepB-IPV	Pediarix		GlaxoSmithKline	**0**	**0**
DTaP-IPV-Hib	Pentacel		sanofi pasteur	**0**	0
DTaP-Hib	TriHIBit		sanofi pasteur	*	*
DTwP	All Products			.01%	25
DT	Diphtheria & Tetanus Toxoids Adsorbed USP	multi-dose	sanofi pasteur	.01%	25
		single dose		*	*
Td	DECAVAC		sanofi pasteur	*	*
	Tetanus and Diphtheria Toxoids Adsorbed		sanofi pasteur	*	*
Tdap	ADACEL		sanofi pasteur	**0**	**0**
	Boostrix		GlaxoSmithKline	**0**	**0**
Tetanus Toxoid	Tetanus Toxoid Adsorbed USP		sanofi pasteur	.01%	25
	Tetanus Toxoid Adsorbed Adult Use			.01%	25
	Booster			.01%	25
Hib	ActHIB		sanofi pasteur	**0**	**0**
	HibTITER		Wyeth-Ayerst	**0**	**0**
	PedvaxHIB liquid(2)		Merck	**0**	**0**
Hib/HepB	Comvax (3)		Merck	**0**	**0**
Hepatitis A	Havrix		GlaxoSmithKline	**0**	**0**
	Vaqta adult/pediatric		Merck	**0**	**0**
Hepatitis B	Engerix-B preservative free		GlaxoSmithKline	**0**	**0**
	Recombivax HB preservative free		Merck	**0**	**0**
Hep A-B	Twinrix		GlaxoSmithKline	**0**	**0**
HPV	Gardasil		Merck	**0**	**0**
Influenza 2008/9 Formula	Afluria	multi-dose	CSL Limited	.01%	24.5
		single dose		**0**	**0**
	Fluarix		GlaxoSmithKline		≤1
	FluLaval		GlaxoSmithKline	.01%	25
	FluMist		MedImmune	**0**	**0**
	Fluvirin		Novartis	.01%	24.5
	Fluzone	5 mL vial	sanofi pasteur	.01%	25
		No Preservative		**0**	**0**
IPV	IPOL		sanofi pasteur	**0**	**0**
Meningococcal	Menactra		sanofi pasteur	**0**	**0**
	MENOMUNE-A/C/Y/W-135	multi-dose	sanofi pasteur	.01%	25
		single dose		**0**	**0**
MMR	M-M-R II		Merck	**0**	**0**
MMR-Varicella	ProQuad		Merck	**0**	**0**
Polio	IPOL		sanofi pasteur	**0**	**0**
Pneumococcal	Prevnar		Wyeth-Ayerst	**0**	**0**
	Pneumovax 23		Merck	**0**	**0**
Rabies	RabAvert		Chiron	**0**	**0**
	IMOVAX		sanofi pasteur	**0**	**0**
Rotavirus	RotaTeq		Merck	**0**	**0**
Typhoid Fever	Typhim Vi		sanofi pasteur	**0**	**0**
	Vivotif		Berna Biotch	**0**	**0**
Varicella Zoster	Varivax		Merck	**0**	**0**
	Zostavax		Merck	**0**	**0**
Yellow Fever	YF-VAX		sanofi pasteur	**0**	**0**

1. A concentration of 1:10,000 is equivalent to a 0.01% concentration. Thimerosal is approximately 50% Hg by weight. A 1:10,000 concentration contains 25 mcg of Hg per 0.5 mL.
2. A previously marketed lyophilized preparation contained 0.005% thimerosal
3. COMVAX is not approved for use under 6 weeks of age because of decreased response to the Hib component

* This product should be considered equivalent to thimerosal-free products. This vaccine may contain trace amounts (<0.3 mcg) of mercury left after post-production thimerosal removal; these amounts have no biological effect. JAMA 1999;282(18) and JAMA 2000;283(16).

Pediatric/VFC Vaccine Price List

Vaccine	Brandname/ Tradename	Packaging	CDC Cost/Dose	Private Sector Cost/Dose	Contract End Date	Manufacturer
DTaP [1]	Tripedia® DAPTACEL®	10 pack - 1 dose vials 10 pack - 1 dose vials	$13.25 $13.75	$22.35 $23.03	03/31/2010	Sanofi Pasteur
DTaP [1]	Infanrix®	10 pack - 1 dose vials 5 pack - 1 dose T-L syringes. No Needle	$13.75 $13.75	$20.96 $21.44	03/31/2010	GlaxoSmithKline
DTaP-IPV [2]	Kinrix®	10 pack - 1 dose vials 5 pack - 1 dose T-L syringes	$32.25 $32.25	$48.00 $48.00	03/31/2010	GlaxoSmithKline
DTaP-Hep B-IPV [4]	Pediarix®	10 pack - 1 dose vials 5 pack - 1 dose T-L syringes. No Needle	$48.75 $48.75	$70.72 $70.72	03/31/2010	GlaxoSmithKline
DTaP-IP-HI [4]	Pentacel®	5 pack - 1 dose vials	$51.49	$72.91	03/31/2010	Sanofi Pasteur
DTaP-Hib [2]	TriHIBit®	5 pack - 1 dose vials	$27.31	$44.88	03/31/2010	Sanofi Pasteur
e-IPV [5]	IPOL®	10 dose vials 10-pack – 1 dose syringes, No Needle	$11.51 $11.51	$23.90 $27.62	03/31/2010	Sanofi Pasteur
Hepatitis B-Hib [3]	COMVAX®	10 pack - 1 dose vials	$28.80	$43.56	03/31/2010	Merck
Hepatitis A Pediatric [5]	VAQTA®	10 pack - 1 dose vials	$13.00	$30.37	03/31/2010	Merck
Hepatitis A Pediatric [5]	Havrix®	10 pack - 1 dose vials 5 pack - 1 dose T-L syringes. No Needle	$12.75 $12.75	$27.41 $27.41	03/31/2010	GlaxoSmithKline
Hepatitis A-Hepatitis B 18 only [3]	Twinrix®	10 pack - 1 dose vials 5 pack - 1 dose T-L syringes, No Needle	$41.50 $41.50	$78.16 $78.42	03/31/2010	GlaxoSmithKline
Hepatitis B [5] Pediatric/Adolescent	ENGERIX B®	10 pack - 1 dose vials 5 pack - 1 dose T-L syringes, No Needle	$9.75 $9.75	$21.37 $21.37	03/31/2010	GlaxoSmithKline
Hepatitis B [5] Pediatric/Adolescent	RECOMBIVAX HB®	10 pack - 1 dose vials	$10.00	$23.20	03/31/2010	Merck

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Hib [5]	PedvaxHIB®	10 pack - 1 dose vials	$11.29	$22.77	03/31/2010	Merck
Hib [5]	ActHIB®	5 pack - 1 dose vials	$8.66	$22.83	03/31/2010	Sanofi Pasteur
HPV - Quadrivalent Human Papillomavirus Types 6, 11, 16 and 18 Recombinant [5]	Gardasil®	10 pack – 1 dose vials	$105.58	$130.27	03/31/2010	Merck
Measles, Mumps, Rubella and Varicella (MMR-V) [2]	ProQuad®	10 pack - 1 dose vials	$82.67	$128.90	03/31/2010	Merck
Meningococcal Conjugate (Groups A, C, Y and W-135) [5]	Menactra®	5 pack - 1 dose vials	$80.13	$98.52	03/31/2010	Sanofi Pasteur
Measles, Mumps and Rubella (MMR) [1]	MMRII®	10 pack - 1 dose vials	$18.30	$48.31	03/31/2010	Merck
Pneumococcal 7-valent [5] (Pediatric)	Prevnar®	10 pack – 1 dose syringes, No Needle	$71.04	$83.88	03/31/2010	Wyeth/Lederle
Rotavirus, Live, Oral, Pentavalent [5]	RotaTeq®	10 pack - 1 dose 2mL tubes	$57.20	$69.59	03/31/2010	Merck
Rotavirus, Live, Oral, Oral [5]	Rotarix®	10 pack - 1 dose vials	$83.25	$102.50	03/31/2010	GlaxoSmithKline
Tetanus & Diphtheria Toxoids [3]	DECAVAC®	10 pack - 1 dose syringes No Needle 10 pack – 1 dose vials	$18.17 $18.17	$19.49 $19.49	03/31/2010	Sanofi Pasteur
Tetanus & Diphtheria Toxoids [3]	MassBiologics	10 pack - 1 dose vials	$15.00		03/31/2010	MassBiologics
Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis [1]	BOOSTRIX®	10 pack - 1 dose vials 5 pack - 1 dose TL syringes, No Needle	$30.75 $30.75	$37.55 $37.55	03/31/2010	GlaxoSmithKline
Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis [1]	ADACEL®	10 pack - 1 dose vials 5 pack - 1 dose BD Leur-Lok syringes	$30.75 $30.75	$37.43 $37.43	03/31/2010	Sanofi Pasteur
Varicella [5]	Varivax®	10 pack - 1 dose vials	$64.53	$80.58	03/31/2010	Merck

[1] Vaccine cost includes $2.25 dose Federal Excise Tax
[2] Vaccine cost includes $3.00 per dose Federal Excise Tax
[3] Vaccine cost includes $1.50 per dose Federal Excise Tax
[4] Vaccine cost includes $3.75 per dose Federal Excise Tax
[5] Vaccine cost includes $0.75 per dose Federal Excise Tax
[6] Vaccines which contain Thimerosal as a preservative

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These price lists are current as of April 8, 2009
Find current Vaccine Price Lists online at www.cdc.gov/vaccines/programs/vfc/cdc-vac-price-list.htm

Adult Vaccine Price List

Vaccine	Brandname/ Tradename	Packaging	CDC Cost/ Dose	Private Sector Cost/ Dose	Contract End Date	Manufacturer
Hepatitis A Adult [5]	VAQTA®	1 dose vials 10 pack - 1 dose vials	$20.00 $19.75	$63.51 $59.99	6/30/09	Merck
Hepatitis A Adult [5]	Havrix®	10 pack - 1 dose vials 5 pack - 1 dose T-L syringes, No Needle	$18.99 $18.99	$60.69 $60.69	6/30/09	GlaxoSmithKline
Hepatitis A-Hepatitis B Adult [3]	Twinrix®	10 pack - 1 dose vials 5 pack - 1 dose T-L syringes, No Needle	$38.64 $38.64	$86.44 $86.44	6/30/09	GlaxoSmithKline
Hepatitis B-Adult [5]	RECOMBIVAX HB®	1 dose vials 10 pack - 1 dose vials 6 pack - 1 dose prefilled syringe	$23.78 $23.372 $25.30	$59.70 $59.09 $61.22	6/30/09	Merck
Hepatitis B-Adult [5]	ENGERIX-B®	10 pack - 1 dose vials 5 pack - 1 dose T-L syringes, No Needle	$24.90 $24.90	$52.50 $52.50	6/30/09	GlaxoSmithKline
Pneumococcal Polysaccharide (23 Valent)	Pneumovax®	1 pack - 5 dose vials 10 pack – single dose 0.5 mL vials	$16.26 $18.93	$32.99 $37.03	6/30/09	Merck
Tetanus & Diphtheria Toxoids [3]	Tetanus & Diphtheria Toxoids Adsorbed for Adults No Preservative	10 pack - 1 dose vials	$13.50	$18.23	6/30/09	MassBioLogics (Akorn, Inc)
Zoster Vaccine Live	Zostavax®	10 pack - 1 dose vial 1 pack-single dose 0.65mL vials	$107.67 $113.16	$153.93 $161.50	6/30/09	Merck

[1] Vaccine cost includes $2.25 dose Federal Excise Tax
[2] Vaccine cost includes $3.00 per dose Federal Excise Tax
[3] Vaccine cost includes $1.50 per dose Federal Excise Tax
[4] Vaccine cost includes $3.75 per dose Federal Excise Tax
[5] Vaccine cost includes $0.75 per dose Federal Excise Tax
[6] Vaccines which contain Thimerosal as a preservative

Pediatric Influenza Vaccine Price List

Vaccine	Brandname/ Tradename	Packaging	CDC Cost/ Dose	Private Sector Cost/ Dose	Contract End Date	Manufacturer
Influenza [5] (Age 6 months and older)	Fluzone®	10 dose vials	$9.09	$11.17	2/28/2010	Sanofi Pasteur
Influenza [5] (Age 6-35 months)	Fluzone® Pediatric dose No Preservative	10 pack - 1 dose syringes	$11.05	$13.16	2/28/2010	Sanofi Pasteur
Influenza [5] (Age 36 months and older)	Fluzone® No-Preservative	10 pack - 1 dose syringes 10 pack – 1 dose vials	$10.31 $10.31	$12.41 $12.41	2/28/2010	Sanofi Pasteur
Influenza [6] [5] (Age 4 years and older)	Fluvirin® Fluvirin® Preservative-free	10 dose vials 10 pack-1 dose syringes	$7.75 $8.50	$9.75 $11.25	2/28/2010 2/28/2010	Novartis Novartis
Influenza [5] Live, Intranasal (Age 2-49 years)	FluMist® No Preservative	10 pack – 1 dose sprayers	$15.25	$19.70	2/28/2010	MedImmune

[5] Vaccine cost includes $0.75 per dose Federal Excise Tax
[6] Vaccines which contain Thimerosal as a preservative

Appendix B

Foreign Language Terms

Aids to translating foreign immunization records.

Table 1: **Disease, Vaccine, and Related Terms.** This table lists terms for vaccine-preventable diseases, vaccines, and other items that might be found on an immunization record, by language.

Table 2: **Trade Names.** This table lists the names of specific vaccines that are used, or have been used, internationally, along with the manufactuer and country or region, when known.

These tables have been adapted from lists developed by
the Minnesota Department of Health Immunization Program
(now maintained by the Immunization Action Coalition)
and the
Washington State Department of Health.

See also:
http://www.immunize.org/izpractices/p5120.pdf
http://www.immunize.org/izpractices/p5121.pdf
http://www.doh.wa.gov/cfh.immunize/documents/schmanul.pdf (Appendix E)

These lists are not comprehensive and, while we have checked and rechecked sources, we do not claim complete accuracy.

Foreign Vaccines

Table 1: Disease, Vaccine, and Related Terms

Albanian	
Difteria	Diphtheria
Fruthi	Measles
Pertusisi	Pertussis
Tetanozi	Tetanus
Arabic	
Alhasiba	Rubella
As'al	Pertussis
Athab	Mumps
Difteria	Diphtheria
El Safra	Hepatitis
Has 'ba	Measles
Shel'el	Polio
Bosnian	
Beseže	BCG
Detepe	DPT
Difterija	Diphtheria
Dječja paraliza	Polio
Gripa	Influenza
Male boginje	Rubella
Ospice	Measles
Rubeola	Rubella
Upala pluća	Pneumonia
Veliki boginje	Smallpox
Veliki kašalj	Pertussis
Zauške	Mumps
Žutica	Hepatitis
Croatian	
Beseže	BCG
Detepe	DTP
Difterija	Diphtheria
Dječja paraliza	Polio
Gripa	Influenza
Hri pavac	Pertussis
Kašalj hripavac	Pertussis
Upala pluća	Pneumonia
Veliki boginje	Smallpox
Vodene kozice	Varicella
Zapaljenje	Hepatitis
Zaušnjaci	Mumps
Žutica	Hepatitis
Czech	
Davivy Kasel	Pertussis
Difterie	Diphtheria
Hepatitida	Hepatitis
Parotitida	Mumps
Pertuse	Pertussis
Poliomyelitis	Polio
Plané Nestovice	Chickenpox
Spalnicky	Measles
Subinuira	Influenza
Zardenky	Rubella
Zaškrt	Diphtheria
Zlutá Zimnice	Yellow Fever
Danish	
Bornelammelse	Polio
Difteritis	Diphtheria
DKTP	DTP + IPV
Faaresyge (Fåresyge)	Mumps
Kighoste	Pertussis
Leverbetaendelse	Hepatitis
Meslinger	Measles
MFR	MMR
Rode Hunde	Rubella
Stivkrampe	Tetanus
Dutch	
BMR	MMR
Bof	Mumps
Difterie	Diphtheria
Gelekoorts	Yellow Fever
Gordelroos	Varicella
Griep	Influenza
Kinderverlamming	Polio
Kinkhoest	Pertussis
Longontsteking	Pneumonia
Mazelen	Measles
Pokken	Smallpox
Rode hond	Rubella
Stijfkramp	Tetanus
Tering	Tuberculosis
Waterpekkea	Chickenpox
Ethiopian (Oromiffaa)	
Cufaa	Tetanus
Difteeriyaa	Diphtheria
Gifira	Measles
Gifira farangli	Rubella
Laamsheesaa	Polio
Qakkee	Pertussis
Shimbiraa	Hepatitis
Finnish	
Hinkuyska	Pertussis

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Jaykkakouristus	Tetanus
Kurkkumata	Diphtheria
Lapsihalvaus	Polio
Sikotauti	Mumps
Tuhkarokko	Measles
Vihurirokko	Rubella
French	
Coqueluche	Pertussis
Diphtérie	Diphtheria
DTC, DT Coq	DTP
Fievre jaune	Yellow Fever
Grippe	Influenza
l'Haemophilus b	Hib
Oreillons	Mumps
Poliomyélite	Polio
ROR	MMR
Rougeole	Measles
Rubéole	Rubella
Tétanos	Tetanus
Tuberculose	Tuberculosis
Variole	Smallpox
German	
Diphtherie	Diphtheria
FSME	Tick-borne encephalitis
Gelbfieber	Yellow Fever
Grippe	Influenza
Keuchhusten	Pertussis
Kinderlähmung	Polio
Masern	Measles
Pocken	Smallpox
Röteln	Rubella
Starrkramph	Tetanus
Tuberkulose	Tuberculosis
Wundstarrkrampf	Tetanus
Zei Genpeter	Mumps
Greek	
Διφθερίτιδα, Τέτανος και Κοκκύτης	DTP
Ο Αιμόφιλος της γρίπτης τύπου B	Hib
Μηνιγγοκοκκική Ασθένεα ομάδας C	Meningococcal C
Ιλαρά - Μαγουλάδες – Ερυθρά	MMR
Πολιομυελίτιδα	Polio
Τέτανος και Διφθερίτιδα	Td
Haitian Creole	
Difteri	Diphtheria
Epatit	Hepatitis
Flou	Influenza
Koklich	Pertussis
Lawoujòl, Laroujòl	Measles
Malmouton	Mumps

Polyo	Polio
Ribeyòl	Rubella
Saranpyon	Varicella
Tetanòs	Tetanus
Hmong	
Hawb pob	Pertussis
Kabmob siab hom B	Hepatitis B
Kub cer	Diphtheria
Qhua Maj	Rubella
Qhua Pias	Measles
Qog	Mumps
Tuag tes tuag taw	Polio
Ua npuag	Tetanus
Indonesian	
Batuk rejan	Pertussis
Beguk	Mumps
Biring Peluh	Rubella
Campak	Measles
Difteri	Diphtheria
Penyakit lumpuh	Polio
Radang hati	Hepatitis
Italian	
Antipolio inattivato	IPV
Difterite	Diphtheria
Emofilo b	Hib
Epatite	Hepatitis
Febbre Giallo	Yellow Fever
Morbillo	Measles
MPR (morbillo, parotite, rosolia)	MMR
Parotite	Mumps
Pertosse	Pertussis
Poliomielite	Polio
Polmonite	Pneumonia
Rosolia	Rubella
Tetano	Tetanus
Tosse Asinina	Pertussis
Tubercolosi	Tuberculosis
Vaioloso	Smallpox
Japanese	
A 型肝炎	Hepatitis A
B 型肝炎	Hepatitis B
Fushin (風疹)	Rubella
Hashika (麻疹 or はしか)	Measles
Hashofu (破傷風)	Tetanus
Hyakaseki (百日咳)	Pertussis
Jifuteria (ジフテリア)	Diphtheria
Otafukukuaze (流行性耳下腺炎 or おたふくかぜ)	Mumps
Sh naimahi (ポリオ)	Polio

三種混合	DTaP
水痘 or みずぼうそう	Varicella
肺炎球菌	Pneumococcal
インフルエンザ菌	Hib
日本脳炎	Japanese Encephalitis
インフルエンザ	Influenza
ツベルクリン	PPD
追加接種	Booster
Malay	
Batok rejan	Pertussis
Penyaakit bengok	Mumps
Sakit champak	Measles
Sakit rengkong	Diphtheria
Norwegian	
Difteri	Diphtheria
Kikhoste	Pertussis
Kopper	Smallpox
Kusma	Mumps
Leverbetennelse	Hepatitis
Meslinger	Measles
Poliomyelitt	Polio
Røde hunder	Rubella
Stivkrampe	Tetanus
Vannkopper	Varicella
Polish	
Błonicy, Błonica, Błonnica	Diphtheria
Dyfteria	Diphtheria
Gruzlica	Tuberculosis
Grypa	Influenza
Koklusz	Pertussis
Krztuscowi, Krztusiec	Pertussis
Odra	Measles
Ospa	Smallpox
Ospa Wietrzna	Chickenpox
Paraliz dzieciecy	Polio
Pojar German	Rubella
Pojarul, Pojarului	Measles
Przypominajace	Booster
Rozyczka	Rubella
Swinka	Mumps
Tezec, Tężcowi	Tetanus
Zapalenie pluc	Pneumonia
Zapalenie watroby	Hepatitis
Zólta Goraczka	Yellow Fever
Portugese	
Cachumba (papeira)	Mumps
Coqueluche	Pertussis
Difteria	Diphtheria
Febre Amarela	Yellow Fever

Gripe	Influenza
Hepatite	Hepatitis
Paralisia infantil	Polio
Parotidite epidémica	Mumps
Poliomielite	Polio
Rúbéola	Rubella
Sarampo	Measles
Tetânica, Tétano	Tetanus
Triplice	DTP
VAHB	Hepatitis B Vaccine
VAP	Polio Vaccine
Varicela	Chickenpox
VAS	Measles Vaccine
VASPR	MMR
VAT	Tetanus Vaccine
Romanian	
AR	Measles
Difteria (Difteriei)	Diphtheria
Di Te	DT
Di-Te-Per	DTP
Febra Galbena	Yellow Fever
Gripa	Influenza
Hepatita	Hepatitis
Holera	Cholera
Oreion, Oreionului	Mumps
Pneumoniei	Pneumonia
Poliomielitic	Polio
Rubeolei, Rubeola	Rubella
Rujeola, Rujeolei	Measles
Tetanos,Tetanosul, Tetanosului	Tetanus
Tuse convulsiva, Tusei convulsive	Pertussis
Varicelă, Varicelei	Varicella
Variola, Variolei	Smallpox
Russian	
Бцж	BCG
АКДС	DTP
Дифтерит, Дифтерия	Diphtheria
Гемоифлюс инфлюзнцы типа Б	Hib
Гепатит	Hepatitis
Грипп	Influenza
Корь	Measles
Свинка, Паротит	Mumps
Коклюш	Pertussis
Воспале лёгких Пневмония	Pneumonia
Полиомиелит	Polio
Краснуха	Rubella
Оспа	Smallpox
Столбняк, Столбняка	Tetanus
Туберкулез	Tuberculosis

Ветрянка	Varicella
Манту	Mantoux (TB Test)
Вакцина	Vaccine
Вакцинация	Series
Ревакцинация	Booster
Samoan	
Mami	Mumps
Misela	Measles
Rupela	Rubella
Serbian	
Beseže	BCG
Detepe	DTP
Difterija	Diphtheria
Dječja paraliza	Polio
Gripa	Influenza
Hri pavac	Pertussis
Male boginje	Rubella
Pljuskavice, Kozice	Varicella
Upala pluća	Pneumonia
Veliki boginje	Smallpox
Veliki kašalj	Pertussis
Zapaljenje	Hepatitis
Zaušnjaci	Mumps
Žutica	Hepatitis
Slovak	
Chripka	Influenza
Cierny kasel	Pertussis
Diftéria	Diphtheria
DiTePe	DTP
Hepatitida	Hepatitis
Krzamak	Measles
Osypky	Measles
Parotitis	Mumps
Polyomyelitida	Polio
Priusnica	Mumps
Ruzienka	Rubella
Zápal' plüc	Pneumonia
Záskrt	Diphtheria
Spanish	
Cólera	Cholera
Coqueluche	Pertussis
Difteria	Diphtheria
Doble Antigen	Td (Mexico)
Doble Viral	Measles-Rubella (Mexico)
Duple	DT (Cuba)
Gripe	Influenza
Hemófilo tipo b	Hib
Numonía	Pneumonia
Paperas, Parotiditis	Mumps

Poliomielitis	Polio
Pulmonía	Pneumonia
Rubéola	Rubella
Sarampión, Sarampión Comun	Measles
Sarampión Aleman	Rubella
SPR	MMR
Tetánica, Tétano	Tetanus
Tos Ferina	Pertussis
Varicela	Varicella
Viruela	Smallpox
Somali	
Bus-buska	Varicella
Cagaarshowga	Hepatitis
Cuno xanuun	Diphtheria
Dabayl	Polio
Duf	Polio
Furuq	Smallpox
Gowracato	Diphtheria
Gurra dhaabsis	Mumps
Hablobaas	Varicella
Haemophilus nooca b	Hib
Infilowense	Influenza
Jadeeco	Measles
Jadeeco been, Jadeeco jarmalka	Rubella
Joonis	Hepatitis
Kix	Pertussis
Qaamow-Qashiir	Mumps
Qaaxo-Tiibi	Tuberculosis
Qanja Barar	Mumps
Sambabaha	Pneumonia
Tallaakla Qaaxada	BCG
Taytano	Tetanus
Wareento	Pneumonia
Xiiqdheer	Pertussis
Swedish	
Difteri	Diphtheria
Duplex	DT
Gula Febern	Yellow Fever
Kikhosta	Pertussis
Kolera	Cholera
Mässling, Masslingormerly	Measles
Påssjura	Mumps
Polio	Polio
Röda Hund	Rubella
Smittkoppor	Smallpox
Stelkramp	Tetanus
Trippel	DTP
Tagalog	
Beke	Mumps
Dipterya	Diphtheria

Pertusis	Pertussis
Polyo	Polio
Tetano	Tetanus
Tigdas	Measles
Turkish	
Boğmaca	Pertussis
Çocuk Felci	Polio
DBT	DPT
Difteri	Diphtheria
Erken Yaz-Beyin Iltihabı'na	Tick-borne encephalitis
Grip	Influenza
KKK	MMR
Kabakulak	Mumps
Kızamık	Measles
Kımamıkçık	Rubella
Meningekoklar	Meningococcal
Kuduz	Rabies
Pnömokoklar	Pneumococcal
Su Çiçeği	Varicella
Tetanos	Tetanus
Ukranian	
Кір	Measles
Полio	Polio
Стовóняк	Tetanus
Vietnamese	
Bach Hâu	Diphtheria
Bai liet	Polio
Ban Đo	Rubella
Dai	Rabies
Ho Gà	Pertussis
Quai Bi	Mumps
Sài Uon Ván	Tetanus
So'i	Measles
Sot Tê Liêt	Polio
Thuong hàn	Typhoid
Uon ván	Tetanus
Viêm gan siêu vi B (VGSV B)	Hepatitis B
VNNB	Japanese encephalitis

April 2009

Appendix B

Foreign Language Terms

Table 2: Trade Names

Trade name	Antigen(s)	Manufacturer, Country
A.D.T.	Diphtheria, tetanus (adsorbed)	Commonwealth, Australia
A.K.D.S.	Diphtheria, tetanus, pertussis	UK
ACVax	Meningococcal (polysaccharide A & C)	GSK, UK
ACWYVax	Meningococcal (polysaccharide A, C, W, Y135)	GSK, UK
Acelluvax	Pertussis (acellular)	Chiron, Italy
ACTAcel	Diphtheria, tetanus, pertussis, Hib	Sanofi Pasteur, Argentina
Adifteper	Diphtheria, tetanus, pertussis	Ism, Italy
Adinvira A+B	Influenza (whole virus)	Imuna
Adiugrip	Influenza	Sanofi Pasteur
Admun	Influenza (whole virus)	Duncan
Admune GP	Influenza (whole virus)	Duncan
Agrippal	Influenza	Socopharm
AH	Hepatitis B	(Romania)
Aimmugen	Hepatitis A (inactivated)	Chemo-Sero-Therapeutic Resh Inst, Japan
Aldiana	Diphtheria (absorbed)	Sevac, Czech Republic
Alditeana	Diphtheria, tetanus (absorbed)	Sevac, Czech Republic
Alditerpera	Diphtheria, tetanus (adsorbed), pertussis	Sevac, Czech Republic
Almevax	Rubella	Evans
Alorbat	Influenza (whole virus)	Asta Pharma
Alteana Sevac	Tetanus	Institute of Sera and Vaccines
Amaril	Yellow fever	Sanofi Pasteur, France
AmBirix	Hepatitis A, Hepatitis B	GSK, Europe
AMC	Hib (polysaccharide)	Cuba
Anadifterall	Diphtheria (adsorbed)	Chiron, Italy
Anatetall	Tetanus (adsorbed)	Chiron, Italy
Anatoxal Di Te	Diphtheria, tetanus	Berna Biotech, Europe
Anatoxal Di Te Per	Diphtheria, tetanus, pertussis	Berna Biotech, Europe
AP	Polio	(Romania)
Arilvax	Yellow fever	MEDI, UK
ATPA	Tetanus Toxoid	(Romania)
AVAC-1, AVA	Anthrax	(for U.S. military use)
AVAXIM	Hepatitis A	Aventis Pasteur, France
B-Hepavac II	Hepatitis B	Merck, Singapore

Trade name	Antigen(s)	Manufacturer, Country
Begrivac	Influenza (split virus)	Chiron, Germany
Betagen	Hepatitis B	Sanofi Pasteur
Biaflu Zonale	Influenza (whole virus)	Farmabiagini, Itali
Biken-HB	Hepatitis B	Biken, Japan
Bilive	Hepatitis A/Hepatitis B (Recombinant)	Sinovac, China
Bimmugen	Hepatitis B (recombinant, adsorbed, yeast derived)	Chemo-Sero-Therapeutic Resh Inst, Japan
Biviraten Berna	Measles, mumps (live)	Berna Biotech, Switzerland
Buccopol Berna	Polio (oral)	Berna Biotech, Europe
BVAC	Botulinum antitoxin	(for U.S. military use)
B-Vaxin	Hepatitis B	Laboratorios Pablo Cassara, Argentina
C.D.T.	Diphtheria, tetanus (pediatric, adsorbed)	Commonwealth, Australia
CEF	Measles (Schwarz strain)	Chiron, Italy
Cacar	Smallpox	Indonesia
Campak Kerig	Measles	Pasteur Institute, Indonesia
Celluvax	Pertussis (acellular)	Chiron, Italy
Cinquerix	Diphtheria, tetanus, pertussis, Hib, Polio	GSK, Europe
Cocquelucheau	Pertussis (adsorbed)	Sanofi Pasteur, France
D-Immun	Diphtheria	Osterreichisches Institut, Austria
D.S.D.P.T.	Diphtheria, tetanus, pertussis (adsorbed)	Dong Shin Pharm, Korea
D.T. Bis Rudivax	Diphtheria, tetanus, rubella	Sanofi Pasteur, France
Di Anatoxal	Diphtheria	Berna Biotech, Europe
Di Te Per Pol Impfstoff	Diphtheria, tetanus, pertussis, polio	Berna Biotech, Switzerland
Di-Te-Pol SSI	Diphtheria, tetanus, polio	Statens Seruminstitut, Denmark
Dif-Tet-All	Diphtheria, tetanus	Chiron, Italy
Diftavax	Diphtheria, tetanus	Sanofi Pasteur
Ditanrix	Diphtheria, tetanus	GSK, Europe
DiTe Anatoxal	Diphtheria, tetanus (adsorbed)	Berna Biotech, Switzerland
Ditoxim	Diphtheria, tetanus (adsorbed)	Dong Shin Pharm, Korea
Double Anigen B.I.	Diphtheria, tetanus	Bengal Immunity Co, India
DT Adulte	Diphtheria, tetanus (adult)	Sanofi Pasteur, France
DT Bis	Diphtheria, tetanus (booster)	Sanofi Pasteur, France
DT Coq	Diphtheria, tetanus, pertussis	Sanofi Pasteur, France
DT Polio	Diphtheria, tetanus, polio	Sanofi Pasteur, France
DT TAB	Diphtheria, tetanus, *Salmonella typhi, Paratyphi A & B*	Sanofi Pasteur, France
DT Vax	Diphtheria, tetanus (pediatric)	Sanofi Pasteur, France

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Trade name	Antigen(s)	Manufacturer, Country
DT Wellcovax	Diphtheria, tetanus (pediatric)	Chiron, UK
Dual Antigen Sii	Diphtheria, tetanus (adsorbed)	Serum Institute of India (Sii)
Dultavax	Diphtheria, tetanus, polio	Aventis Pasteur, France
Dupla	Diphtheria, tetanus	Instituto Butantan, Brazil
Duplex	Diphtheria, tetanus	Sweden
Ecolarix	Measles, rubella (Schwarz & RA 27/3)	GSK, Europe
Elvarix	Influenza (split virus)	VEB Sachsesches Serumwerk Dresden
Encepur	Tick-borne encephalitis	Chiron, Europe
Enivac-HB	Hepatitis B (Recombinant DNA)	Centro de Ingenieria Genetica Y Biotecnologia, Cuba
Enterovaccino	Typhoid (IM)	Isi
Enzira	Influenza	CSL
Eolarix	Measles, rubella (Schwarz & RA 27/3)	GSK, Europe
Epaxal Berna	Hepatitis A - virosomal vaccine	Berna Biotech, Switzerland
Ervax	Rubella (live)	GSK, Mexico
Ervevax RA 27/3	Rubella (live)	GSK, Belgium
Esavalenti	Diphtheria, tetanus, pertussis, polio, Hib, hepatitis B	Italy
Euvax-B	Hepatitis B (recombinant DNA)	LG Chemical, South Korea
Fendrix	Hepatitis B (dialysis formulation)	GSK, Europe
Fluad Agrippal-S1	Influenza	Chiron, Italy
Flubron	Influenza (whole virus)	Pfizer
Flugen	Influenza	UK
Fluvax	Influenza	CSL, Australia
Fluvirine	Influenza	CellTech Pharma SA
FOH-M	Polio (Inactivated)	Russia
FrocuoOke	Polio (Inactivated)	Russia
FSME-IMMUNE	Tick-borne encephalitis	Baxter, Austria
FSPD	Measles	Russia
Funed-CEME	Diphtheria, tetanus, pertussis	Belo Horizonte, Brazil
Gen H-B-Vax	Hepatitis B	Merck-Behringwerke
GenHevac B Pasteur	Hepatitis B	Sanofi Pasteur
Gene Vac-B	Hepatitis B	Serum Institute of India (Sii)
Gripax	Influenza (whole virus)	Hebrew University
Gripe	Influenza (whole virus)	Spain
Gripovax	Influenza (whole virus)	GSK
Gunevax	Rubella	Chiron, Italy

Trade name	Antigen(s)	Manufacturer, Country
H-Adiftal	Diphtheria	Ism, Italy
H-Adiftetal	Diphtheria, tetanus (adult)	Ism, Italy
H-Atetal	Tetanus	Ism, Italy
HarPaBreHnr B CtauOHAP	Rubella	Russia
HAVPur	Hepatitis A	Chiron, Germany
HB Vax Pro	Hepatitis B	SP
HBY	Hepatitis B (recombinant)	KGC, Japan
Heberbiovac HB	Hepatitis B	Heberbiotec, Cuba
Hepabest	Hepatitis A	Sanofi Pasteur, Mexico
Hepacare	Hepatitis B (recombinant)	Chiron, Europe
Hepaccine-B	Hepatitis B (plasma derived)	Chiel Jedang, South Korea
Hepagene	Hepatitis B	Chiron, Europe
Hepativax	Hepatitis B	LG Life Sciences, Korea
Hepavax-B	Hepatitis B (plasma derived)	Korea Green Cross, South Korea
Hepavax-Gene	Hepatitis B (recombinant DNA)	Korea Green Cross, South Korea
Hepcare	Hepatitis B	Chiron, Europe
Heprecomb	Hepatitis B (yeast derived)	Berna Biotech, Switzerland
Hevac B	Hepatitis B (plasma derived)	Sanofi Pasteur, France
Hexavac (Hexavax)	Diphtheria, tetanus, pertussis, polio, hepatitis B, Hib	Sanofi Pasteur, Europe
Hiberix	Hib conjugate	GSK
HIBest	*Haemophilus influenzae* type b	Sanoti Pasteur
Hinkuys karokoe	Pertussis (adsorbed)	Natl. Public Health Institute, Finland
HIS	Influenza	Serbian Institute, Yugoslavia
IBV	Polio (inactivated)	Statens Seruminstitut, Denmark
Immravax	Measles, mumps, rubella	Sanofi Pasteur, Europe
Immugrip	Influenza	Pierre Fabre Médicament
Immunil	Pneumococcal (polysaccharide)	Sidus
Imovax Parotiditis	Mumps	Sanofi Pasteur, Europe
Imovax Polio	Polio	Sanofi Pasteur, Europe
Imovax Sarampion	Measles	Sanofi Pasteur, Europe
Imovax D.T.	Diphtheria, tetanus (adult)	Sanofi Pasteur, Europe
Imovax Gripe	Influenza	Sanofi Pasteur, Europe
Imovax R.O.R.	Measles, rubella, mumps (live)	Sanofi Pasteur, Europe
Imovax Rubeola	Measles	Sanofi Pasteur, Europe
Imovax Mumps	Mumps	Sanofi Pasteur, Europe

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Trade name	Antigen(s)	Manufacturer, Country
Imovax Oreillons	Mumps	Sanofi Pasteur, Europe
Imovax Rage	Rabies vaccine	Sanofi Pasteur, Europe
Imovax Tetano	Tetanus	Sanofi Pasteur, Europe
Infanrix Hexa	DTaP, polio, Hib, hepatitis B	GSK, France
Infanrix Penta	DTaP, hepatitis B, polio	GSK, Europe
Infanrix Quinta	DTaP, polio, Hib	GSK, Europe
Infanrix Tetra	DTaP, polio	GSK, Europe
Inflexal	Influenza	Swiss Serum and Vaccine Institute
Influmix	Influenza (whole virus)	Schiapparelli
Influpozzi Zonale	Influenza (whole virus)	Ivp
Influsplit SSW	Influenza (split virus)	VEB Sachsecsches Serumwerk Dresden
Influvac	Influenza	Solvay-Pharma
Influvirus	Influenza	Ism, Italy
Invirin	Influenza (whole virus)	GSK
Ipad TP	Tetanus, polio	Sanofi Pasteur, France
IPV-Virelon	Polio (inactivated)	Chiron, Europe
Isiflu Zonale	Influenza (whole virus)	Isi, Italy
Istivac	Influenza	Sanofi Pasteur, Europe
Kaksoisrokote Dubbelvaccin	Diphtheria, tetanus (pediatric)	Natl. Public Health Institute, Finland
Kikhoste-Vaksine	Pertussis	Statens Institutt for Folkehelse, Norway
Koplivac	Measles (Edmonston strain)	Philips-Duphar, Australia
Kotipa	Cholera, typhoid, paratyphoid	Perum Bio Farma, Indonesia
Krztuscowi	Pertussis	(Poland)
Ksztu	Pertussis	(Poland)
Lancy Vaxina	Smallpox	Swiss Serum and Vaccine Institute, Switzerland
Lavantuu tirokote	Typhoid	Central Pub Health La, Finland
Liomorbillo	Measles	
Liovaxs	Smallpox	Chiron, Italy
Lirugen	Measles	Sanofi Pasteur
LM - 3 RIT	Measles, mumps, rubella (live)	Dong Shin Pharm, Korea
LM - 2 RIT	Measles, mumps (live)	Dong Shin Pharm, Korea
Lteanas Imuna	Tetanus (adsorbed)	Imuna sp., Slovakia
Lyssavac N	Rabies	Berna Biotech, Europe
M-M-Rvax	Measles, mumps, rubella	Chiron, Europe
M-M-Vax	Measles, mumps	Merck, Europe
M-Vac	Measles (live)	Serum Institute of India (Sii)

Trade name	Antigen(s)	Manufacturer, Country
Masern-Impfstoff SSW	Measles (live)	Chiron, Germany
Massling	Measles	Sweden
MDPH-PA	Anthrax	
Measavac	Measles (Edmonston strain)	Pfizer, UK
Mencevax A	Meningococcal (polysaccharide) (Group A)	SmithKline/RIT, Belgium
Mencevax ACWY	Meningococcal quadravalent	GSK
Mengivax A/C	Meningococcal (conjugate) (Groups A & C)	Sanofi Pasteur, Europe
Meningitec	Meningococcal (conjugate) (Group C)	Wyeth, UK, Australia
Meningtec	Meningococcal (conjugate) (Group C)	Wyeth, Canada
Meninvact	Meningococcus (conjugate) (Group C)	Sanofi Pasteur
Menjugate	Meningococcus (conjugate) (Group C)	Socopharm
Menpovax 4	Meningococcal (polysaccharide) (Groups A, C, Y & W135)	Chiron, Europe
Menpovax A+C	Meningococcal (Groups A & C)	Chiron, Italy
MeNZB	Meningococcal B	Novartis (New Zealand)
Mesavac	Measles (Edmonston strain)	Pfizer, UK
Mevilin-L	Measles (Schwarz strain)	Chiron, UK
MFV	Influenza (whole virus)	Servier, UK
MFV-Ject	Influenza (whole virus)	Sanofi Pasteur, Europe
Miniflu	Influenza	Schiapparelli, Italy
Mo-Ru Viraten	Measles, rubella	Berna Biotech, Canada
Moniarix	Pneumococcal (polysaccharide)	GSK, Europe
Monovax / Monovac	BCG	Sanofi Pasteur, France
Mopavac	Measles, mumps (live, attenuated)	Sevac, Czech Republic
Morbilvax	Measles (live, attenuated)	Chiron, Italy
Morubel	Measles, rubella (live, attenuated)	Chiron, Italy
Moruman Berna	Measles immunoglobulin	Berna, Switzerland
Morupar	Measles, mumps, rubella (live, attenuated)	Chiron, Italy
Movivac	Measles (live, attenuated)	Sevac, Czech Republic
Mumaten	Mumps (live)	Berna Biogech, Switzerland
Munevan	Influenza (whole virus)	Medeva
Mutagrip	Influenza	Sanofi Pasteur, Germany
Nasoflu	Influenza	GSK, Europe
Neis Vac-C	Meningococcal (conjugate) (Group C)	Baxter, Europe & Canada
Neotyf	Typhoid (oral)	Chiron, Italy
Nilgrip	Influenza`	CSL
Nivgrip	Influenza (whole virus)	Nicolau Institute of Virology, Romania

Appendix B

Trade name	Antigen(s)	Manufacturer, Country
NorHOMHerHTA	Polio (Inactivated)	Russia
Nothav	Hepatitis A	Chiron, Italy
Okavax	Varicella	Sanofi Pasteur, Japan & Europe
Oral Virelon	OPV	Chiron, Germany
Pariorix	Mumps (live)	GSK, Mexico & Europe
Pavivac	Mumps (live)	Sevac, Czech Republic
Pediacel	DTaP, Hib, IPV	Europe
Penta	Diphtheria, tetanus, (acellular) pertussis, Hib, IPV	Sanofi Pasteur, Europe
PENT-HIBest	Diphtheria, tetanus, pertussis, polio, Hib	Sanofi Pasteur
Pentacel	Diphtheria, tetanus, pertussis, polio, Hib	Sanofi Pasteur, Canada
Pentacoq	Diphtheria, tetanus, pertussis, polio, Hib	Sanofi Pasteur
PentAct-HIB	Diphtheria, tetanus, pertussis, polio, Hib	Sanofi Pasteur, Europe
Pentavac	Diphtheria, tetanus, pertussis, polio, Hib	Sanofi Pasteur
Pentavalente	Diphtheria, tetanus, pertussis, hepatitis B, Hib	Mexico
Pentavalenti	Diphtheria, tetanus, pertussis, polio, Hib OR Diphtheria, tetanus, pertussis, polio, hepatitis B	Italy
Pentaxim	Diphtheria, tetanus, pertussis, polio, Hib	Aventis Pasteur, France
Pluserix	Measles, rubella	GSK, Mexico & Europe
Pneumopur	Pneumococcal (polysaccharide)	Chiron, Europe
POLIAcel	Diphtheria, tetanus, pertussis, polio, HIB	Sanofi Pasteur, Argentina
Poliomyelite	Polio (inactivated)	France
Polioral	Polio (oral)	Chiron, Germany
Polio Sabin	Polio (oral)	GSK, Europe
Poloral	Polio (oral)	Swiss Serum and Vaccine Institute
Prevenar	Pneumococcal (7-valent, conjugate)	Wyeth, France
Previgrip	Influenza	Chiron France
Primavax	Diphtheria, tetanus, hepatitis B	Sanofi Pasteur, Europe
Priorix	Measles, mumps, rubella (live)	GSK, Europe & Australia
Priorix-Tetra	Measles, mumps, rubella, varicella	GSK, Europe
Probivac-B	Hepatitis B	Probiomed, Mexico
Procomvax	Hib, hepatitis B	Merck, Sanofi Pasteur, Europe
Pulmovax	Pneumococcal (polysaccharide)	Merck
Q-Vac	Diphtheria, tetanus, pertussis, hepatitia B	Serum Institute of India (Sii)
Quadracel	Diphtheria, tetanus, pertussis, polio	Sanofi Pasteur, Mexico
QUADRAcel/Hibest	Diphtheria, tetanus, pertussis, polio, Hib	Sanofi Pasteur, Argentina
Quadravax	DTP + polio	GSK

Trade name	Antigen(s)	Manufacturer, Country
Quatro-Virelon	Diphtheria, tetanus, pertussis, polio	Chiron, Europe
Quinivax-IN	Diphtheria, tetanus, pertussis, Hib, polio	Valda Laboratori, Europe
Quintuple	Diphtheria, tetanus, pertussis, Hib, Polio	GSK, Mexico
R-HB Vaccine	Hepatitis B (recombinant)	Mitsubishi Chem Corp, Japan
R-Vac	Rubella (live)	Serum Institute of India (Sii)
Rabdomune	Rabies	Impdfstofwerke, Germany
Rabipur	Rabies	Chiron, Germany
Rabivac	Rabies	Chiron, Germany
Rasilvax	Rabies	Chiron, Italy
RDCV	Rabies	
Repevax	DTaP, IPV	Sanofi Pasteur
Revaxis	Td, IPV	Sanofi Pasteur, Europe
Rimevax	Measles (live)	GSK, Mexico & Europe
Rimparix	Measles, mumps (live)	GSK, Europe
RIT - LM-2	Measles, mumps (live)	Dong Shin Pharm, Korea
RIT - LM-3	Measles, mumps, rubella (live)	Dong Shin Pharm, Korea
Rorvax	Measles, mumps, rubella (live)	Sanofi Pasteur, Europe & Brazil
Rosovax	Rubella	Ism, Italy
Rouvax	Measles (live, attenuated)	Sanofi Pasteur, Europe
Rubavax	Rubella (live)	Sanofi Pasteur, UK
Rubeaten	Rubella (live)	Berna Biotech, Europe
Rubellovac	Rubella	Chiron, Germany
Rubilin	Rubella (live)	Chiron, UK
Rudi-Rouvax	Measles, rubella (live)	Sanofi Pasteur, France
Rudivax	Rubella (live, attenuated)	Sanofi Pasteur, Europe
Sahia	Polio (live, oral)	Multiple manufacturers
Sampar	Plague	Sanofi Pasteur, Indonesia
Sandovac	Influenza	Sandoz, Austria
Serap	Diphtheria, tetanus, pertussis	Perum Bio Farma, Indonesia
Shanvac-B	Hepatitis B	Shantha, India
SMBV	Rabies	Sanofi Pasteur, Europe
Sii Rabivax	Rabies	Serum Institute of India (Sii)
Sii Triple Antigen	Diphtheria, tetanus, pertussis	Serum Institute of India (Sii)
Stamaril	Yellow fever (live, attenuated)	Sanofi Pasteur, Europe
Streptopur	Pneumococcal (polysaccharide)	Chiron, Europe
Subinvira	Influenza (split virus)	Imuna. Czech Republic

Appendix B

Trade name	Antigen(s)	Manufacturer, Country
T. Polio	Tetanus toxoid, polio	SP (Canada)
T.A.B.	Typhoid, paratyphoid (A & B)	- Institute Pasteur, Tunisia - Egypt - Pharmaceutical Industries Corp, Burma
T-Immun	Tetanus (adsorbed)	Baxter, Germany
T-Vaccinol	Tetanus	Roehm Pharma, Germany
T-Wellcovax	Tetanus	Wellcopharm, Germany
Tanrix	Tetanus	GSK, Europe
Td-Pur	Tetanus, diphtheria	Chiron, Europe
Td-Virelon	Tetanus, diphtheria, polio	Chiron, Europe
Te Anatoxal	Tetanus	Berna Biotech, Switzerland
Telvaclptap	Tetanus	Yugoslavia
Tet-Aktiv	Tetanus	Tropon-Cutter, Germany
Tet-Tox	Tetanus	CSL Limited, Australia
Tetagrip	Tetanus, influenza	SP (France)
Tetamun SSW	Tetanus (fluid, nonadsorbed)	Veb Sachsisches Serumwerk, Germany
Tetamyn	Tetanus	Bioclon, Mexico
Tetanol	Tetanus (adsorbed)	Chiron, Sanofi Pasteur, Europe & Mexico
Tetanovac	Tetanus	Sanofi Pasteur, Mexico
Tetasorbat SSW	Tetanus (adsorbed)	Veb Sachsisches Serumwerk, Germany
Tetatox	Tetanus (adsorbed)	Berna Biotech, Italy
Tetavax	Tetanus (adsorbed)	Sanofi Pasteur, Europe
Tetracoq 05	Diphtheria, tetanus, pertussis, polio	Sanofi Pasteur, France
TetrAct-HIB	Diphtheria, tetanus, pertussis, Hib	Sanofi Pasteur, Europe
Tetravac Acellulaire	Diphtheria, tetanus, pertussis, polio	Sanofi Pasteur, Europe
Tetravalenti	Diphtheria, tetanus, pertussis, hepatitis B	Italy
Tetraxim	Tetanus, diphtheria, pertussis, polio	Sanofi Pasteur, Europe
Theracys	BCG	Aventis Pasteur, Canada
Ticovac	Tick-borne encephalitis	Baxter SA
Tifovax	Typhoid (Vi polysaccharide)	Sanofi Pasteur, Mexico
Titifica	Typhoid and para typhoid	Italy
TOPV	Trivalent oral polio vaccine	Multiple manufacturers and countries
Trenin DPT Behring	Diphtheria, tetanus, pertussis	Chiron Behring GmbH, Germany
Tresivac	Measles, mumps, rubella	Serum Institute of India (Sii)
Triacel	Diphtheria, tetanus, (acellular) pertussis	Sanofi Pasteur, Europe & Mexico
Triacelluvax	Diphtheria, tetanus, (acellular) pertussis	Chiron, Europe
Trimovax	Measles, mumps, rubella (live)	Sanofi Pasteur, Europe

Trade name	Antigen(s)	Manufacturer, Country
Tripacel	Diphtheria, tetanus, (acellular) pertussis	Sanofi Pasteur, Europe
Triple antigen	Diphtheria, tetanus, pertussis	- Chowgule & Co., India - CSL Limited, Australia
Triple Sabin	Polio (live, oral)	Mexico
Triple	Diphtheria, tetanus, pertussis	Cuba, Mexico
Triple Viral	Measles, mumps, rubella	Mexico Immunology Institute, Croatia
Triplice (VT)	Diphtheria, tetanus, pertussis	Instituto Butantan, Brazil
Triplice Viral (VTV)	Measles, mumps, rubella	Instituto Butantan, Brazil
Triplovax	Measles, mumps, rubella	Sanofi Pasteur, Europe & Brazil
Tritanrix	DTwP	GSK
Tritanrix-HB	DTwP/hepatitis B	GSK, Mexico
Tritanrix-HB-Hib	DTwP/hepatitis B/Hib	GSK
Trivacuna Leti	Diphtheria, tetanus (adsorbed), pertussis	Laboratory Leti, Spain
Trivax	Diphtheria, tetanus (plain), pertussis	Chiron, UK
Trivax-AD	Diphtheria, tetanus (adsorbed), pertussis	Chiron, UK
Trivax-Hib	Diphtheria, tetanus, pertussis, Hib	GSK, Europe
Trivb	Diphtheria, tetanus, pertussis	Brazil
Triviraten	Measles, mumps, rubella (live, attenuated)	Berna Biotech, Switzerland
Trivivac	Measles, mumps, rubella (live, attenuated)	Sevac, Czech Republic
Trivivax	Measles, mumps, rubella	Sanofi Pasteur, Mexico
Tussitrupin Forte	Pertussis	Staatliches Institut, Germany
Tuvax	BCG	Japan BCG Laboratory, Japan
Tyne	BCG	Sweden
Typherix	Typhoid (Vi polysaccharide)	GSK, Europe & Australia
Typhopara-typhoidique	Typhoid and para typhoid	France
Typhoral-L	Typhoid (Ty21a oral)	Berna Biotech, Germany
Typh-Vax	Typhoid	CSL Limited, Australia
Va-Diftet	Diphtheria, tetanus	Finlay Vacunas y Sueros, Cuba
Va-Mengoc-BC	Meningococcal (Groups B & C)	Finlay Vacunas y Sueros, Cuba
Vac-DPT	Diphtheria, tetanus, pertussis	Bioclon, Mexico
Vaccin Difteric Adsorbit	Diphtheria toxoid (adsorbed)	Cantacuzino Institute, Romania
Vaccin Rabique Pasteur	Rabies	Pasteur Vaccins
Vaccin Combinat Diftero-Tetanic	Diphtheria, tetanus (adsorbed)	Cantacuzino Institute, Romania
Vaccin tuberculeux attenue lyophilise	BCG	Sanofi Pasteur, France
Vaccinum Morbillorum Vivum	Measles (live)	Moscow Research Institute, Russia

Appendix B

Trade name	Antigen(s)	Manufacturer, Country
Vacina Dupla	Diphtheria, tetanus	Instituto Butantan, Brazil
Vacina Triplice	Diphtheria, tetanus, pertussis	Instituto Butantan, Brazil
Vacina Triplice Viral	Measles, mumps, rubella	Brazil
Vacunol	Tetanus	Temis-Lostato, Brazil
Vakcin Sampar	Plague	Perum Bio Farma, Indonesia
Vaksin Cacar	Smallpox	Indonesia
Vaksin Serap	Diphtheria, tetanus, pertussis	Perum Bio Farma, Indonesia
Vaksin Campak Kerig	Measles (live, attenuated)	Perum Bio Farma, Indonesia
Vaksin Kotipa	Cholera, typhoid and paratyphoid A, B & C	Perum Bio Farma (Indonesia)
Vamoavax	Measles, mumps (live)	Institute of Immunology, Croatia
Varicella-RIT	Varicella	GSK, Europe
Varicellon	Varicella zoster immunoglobulin	Behringwerke Aktiengesellischaft, Germany
Varie	Smallpox (lyophilized)	Institute of Sera and Vaccine, Czech Republic
Varilrix	Varicella (live, Oka strain)	GSK, Europe & Mexico
Vax-Tet	Tetanus	Finlay Vacunas & Sueros, Cuba
Vaxem-Hib	Hib (polysaccharide)	Chiron, Europe
Vaxicoq	Pertussis (adsorbed)	Sanofi Pasteur, France
Vaxigrip	Influenza	Sanofi Pasteur, Europe & Australia
Vaxihaler-Flu	Influenza (inhaler)	Riker, UK
Vaxipar	Mumps (live)	Chiron, Italy
VCDT	Diphtheria, tetanus (pediatric)	Cantacuzino Institute, Romania
VDA Vaccin Difteric Adsorbit	Diphtheria	Cantacuzino Institut, Romania
Verorab	Rabies (purified vero cell)	Sanofi Pasteur, France
Vibriomune	Cholera	Duncan Flockhart, UK
Viralinte	Hepatitis B	Ivax Pharmaceuticals, Mexico
Virelon C	Polio (Inactivated)	Chiron, Germany
Virelon T 20	Polio (live, oral, trivalent)	Chiron, Germany
Virivac	Measles, mumps, rubella (live)	Merck, Finland
Virovac Massling, Perotid, Rubella	Measles, mumps, rubella	Sweden
Vopix	OPV	PT Biofarma, Indonesia
VT (Vacina Triplice)	Diphtheria, tetanus, pertussis	Instituto Butantan, Brazil
VTV (Vacina Triplice Viral)	Measles, mumps, rubella	Brazil
VVR	Measles (live, attenuated)	Cantucuzino Institute, Romania
Welltrivax trivalente	Diphtheria, tetanus, pertussis	Spain

Trade name	Antigen(s)	Manufacturer, Country
X-Flu	Influenza	CSL
Zaantide	Diphtheria anti-toxin	Imunoloski Zavod, Croatia
Zaantite	Tetanus anti-toxin	Imunoloski Zavod, Croatia
Zaditeadvax	Diphtheria, tetanus	Imunoloski Zavod, Croatia
Zaditevax	Diphtheria, tetanus	Imunoloski Zavod, Croatia
Zamevax A+C	Meningococcal (polysaccharide, Groups A & C)	Imunoloski Zavod, Croatia
Zamovax	Measles (live)	Imunoloski Zavod, Croatia
Zamruvax	Measles, rubella (live)	Imunoloski Zavod, Croatia
Zapavax	Mumps	Imunoloski Zavod, Croatia
Zaruvax	Rubella (live)	Imunoloski Zavod, Croatia
Zatetravax	Diphtheria, tetanus, pertussis, parapertussis	Imunoloski Zavod, Croatia
Zatevax	Tetanus	Imunoloski Zavod, Croatia
Zatribavax	Diphtheria, tetanus, pertussis	Imunoloski Zavod, Croatia
Zatrivax	Measles, rubella, mumps (live)	Imunoloski Zavod, Croatia

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APPENDIX C
Vaccine Storage & Handling

Vaccine Storage & Handling Recommendtions (April 2009) C-1

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Appendix C

VACCINE MANAGEMENT

Recommendations for Storage and Handling of Selected Biologicals

April 2009

Appendix C

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Manufacturer Quality Control Office Telephone Numbers. C-19

DT: Diphtheria, Tetanus Toxoids–Pediatric
Td: Tetanus, Diphtheria Toxoids–Adult

Shipping Requirements
Should be shipped in insulated container.
Maintain temperature at 35° to 46°F (2° to 8°C). *Do not freeze or expose to freezing temperatures.*

Condition upon Arrival
Should not have been frozen or exposed to freezing temperatures. Refrigerate upon arrival.
If you have questions about the condition of the material at the time of delivery, you should 1) immediately place material in recommended storage; and 2) then follow your state health department immunization program policy and contact either the manufacturer's Quality Control office or the immunization program for guidance.

Storage Requirements
Refrigerate immediately upon arrival. Store at 35° to 46°F (2° to 8°C). *Do not freeze or expose to freezing temperatures.*

Shelf Life
Check expiration date on vial or manufacturer-filled syringe.

Instructions for Use
Inspect visually for extraneous particulate matter and/or discoloration. If these conditions exist, the vaccine should not be used. Shake vial or manufacturer-filled syringe well before use. Discard vaccine if it cannot be resuspended with thorough agitation.

Shelf Life After Opening
Single-Dose Vials: The vaccine should be administered shortly after withdrawal from the vial.
Multidose Vials: Withdraw single dose of vaccine into separate sterile needle and syringe for each immunization. The vaccine should be administered shortly after withdrawal from the vial. Unused portions of multidose vials may be refrigerated at 35° to 46°F (2° to 8°C) and used until expired, if not contaminated or unless otherwise stated in the manufacturer's product information.
Manufacturer-Filled Syringes: The vaccine should be administered shortly after the needle is attached to the syringe.

Special Instructions
Rotate stock so that the earliest dated material is used first.
Note: All vaccine materials should be disposed of using medical waste disposal procedures. Contact the state health department for details.

Appendix C

DTaP: Diphtheria Toxoid, Tetanus Toxoid, Acellular Pertussis Vaccine–Pediatric
DTaP/Hib: Diphtheria Toxoid, Tetanus Toxoid, Acellular Pertussis Vaccine Combined with *Haemophilus influenzae* type b Conjugate Vaccine–Pediatric (TriHIBit)
DTaP-IPV: Diphtheria Toxoid, Tetanus Toxoid, Acellular Pertussis Vaccine, Inactivated Polio Vaccine–Pediatric (Kinrix)
DTaP-IPV/Hib: Diphtheria Toxoid, Tetanus Toxoid, Acellular Pertussis Vaccine, Inactivated Polio Vaccine combined with *Haemophilus influenzae* type b Conjugate Vaccine–Pediatric (Pentacel)
DTaP-HepB-IPV: Diphtheria Toxoid, Tetanus Toxoid, Acellular Pertussis Vaccine, Hepatitis B Vaccine, Inactivated Polio Vaccine–Pediatric (Pediarix)
Tdap: Tetanus Toxoid, Diphtheria Toxoid, Acellular Pertussis Vaccine–Adult

Shipping Requirements

Should be shipped in insulated container. Maintain temperature at 35° to 46°F (2° to 8°C). *Do not freeze or expose to freezing temperatures.*

Condition upon Arrival

Should not have been frozen or exposed to freezing temperatures. Refrigerate upon arrival.
If you have questions about the condition of the material at the time of delivery, you should 1) immediately place material in recommended storage; and 2) then follow your state health department immunization program policy and contact either the manufacturer's Quality Control office or the immunization program for guidance.

Storage Requirements

Refrigerate immediately upon arrival. Store at 35° to 46°F (2° to 8°C). ***Do not freeze or expose to freezing temperatures.***

Shelf Life

Check expiration date on vial, container, or manufacturer-filled syringe.

Instructions for Reconstitution*† or Use

Inspect visually for extraneous particulate matter and/or discoloration. If these conditions exist, the vaccine should not be used. Shake vial or manufacturer-filled syringe well before use. Discard vaccine if it cannot be resuspended with thorough agitation.

Shelf Life After Reconstitution*† or Opening

Single-Dose Vials: The vaccine should be administered shortly after withdrawal from the vial.
Manufacturer-Filled Syringes: The vaccine should be administered shortly after the needle is attached to the syringe.

Special Instructions

Rotate stock so that the earliest dated material is used first.
Note: All vaccine materials should be disposed of using medical waste disposal procedures. Contact the state health department for details.

* DTaP/Hib (TriHIBit) is ActHIB (sanofi pasteur) reconstituted with Tripedia (sanofi pasteur). Once reconstituted, this combination vaccine must be used within 30 minutes or discarded. The only DTaP vaccine that can be used to reconstitute the ActHIB for TriHIBit is Tripedia. No other brand of DTaP is approved for this use.

† DTaP-IPV/Hib (Pentacel is ActHIB (sanofi pasteur) reconstituted with a DTaP-IPV solution. Once reconstituted, this combination vaccine must be used within 30 minutes or discarded. This combination arrives with the DTaP-IPV vials and the ActHIB vials packaged together. Do not store them separately and do not administer them separately.

Hepatitis Vaccines:
HepA: Hepatitis A, HepB: Hepatitis B, HepA-HepB: Hepatitis A/B (Twinrix), HepB-Hib: Hepatitis B/*Haemophilus influenzae* type b (Comvax)

Shipping Requirements
Should be shipped in insulated container. Maintain temperature at 35° to 46°F (2° to 8°C). *Do not freeze or expose to freezing temperatures.*

Condition upon Arrival
Should not have been frozen or exposed to freezing temperatures. Refrigerate upon arrival.
If you have questions about the condition of the material at the time of delivery, you should 1) immediately place material in recommended storage; and 2) then follow your state health department immunization program policy and contact either the manufacturer's Quality Control office or the immunization program for guidance.

Storage Requirements
Refrigerate immediately upon arrival. Store at 35° to 46°F (2° to 8°C). *Do not freeze or expose to freezing temperatures.*

Shelf Life
Check expiration date on vial or manufacturer-filled syringe.

Instructions for Use
Inspect visually for extraneous particulate matter and/or discoloration. If these conditions exist, the vaccine should not be used. Shake vial or manufacturer-filled syringe well before use. Discard vaccine if it cannot be resuspended with thorough agitation.

Shelf Life After Opening
Single-Dose Vials: The vaccine should be administered shortly after withdrawal from the vial.
Manufacturer-Filled Syringes: The vaccine should be administered shortly after the needle is attached to the syringe.

Special Instructions
Rotate stock so that the earliest dated material is used first.
Note: All vaccine materials should be disposed of using medical waste disposal procedures. Contact the state health department for details.

Hib: *Haemophilus influenzae* type b Conjugate Vaccine

Shipping Requirements

Should be shipped in insulated container. Maintain temperature at 35° to 46°F (2° to 8°C). *Do not freeze or expose to freezing temperatures.*

Condition upon Arrival

Should not have been frozen or exposed to freezing temperatures. Refrigerate upon arrival.
If you have questions about the condition of the material at the time of delivery, you should 1) immediately place material in recommended storage; and 2) then follow your state health department immunization program policy and contact either the manufacturer's Quality Control office or the immunization program for guidance.

Storage Requirements

Vaccine: Refrigerate immediately upon arrival. Store at 35° to 46°F (2° to 8°C). *Do not freeze or expose to freezing temperatures.*
Diluent: May be refrigerated or stored at room temperature (68° to 77°F [20° to 25°C]). *Do not freeze or expose to freezing temperatures.*

Shelf Life

Check expiration date on vial.

Instructions for Reconstitution* or Use

Inspect visually for extraneous particulate matter and/or discoloration. If these conditions exist, the vaccine should not be used. Shake vial or manufacturer-filled syringe well before use. Discard vaccine if it cannot be resuspended with thorough agitation.

Shelf Life After Opening

Single-Dose Vials: The vaccine should be administered shortly after withdrawal from the vial.

Special Instructions

Rotate stock so that the earliest dated material is used first.
Note: All vaccine materials should be disposed of using medical waste disposal procedures. Contact the state health department for details.

*ActHIB (sanofi pasteur) reconstituted with 0.4% sodium chloride diluent should be used within 24 hours after reconstitution. If sanofi pasteur DTaP-Tripedia is used to reconstitute ActHIB, the TriHIBit vaccine must be used within 30 minutes of reconstitution. Only sanofi pasteur DTaP-Tripedia or the diluent shipped with the product may be used to reconstitute the sanofi pasteur ActHIB product. No other brand of DTaP is licensed for use in reconstitution of ActHIB.

HPV: Human Papillomavirus Vaccine

Shipping Requirements

Should be shipped in insulated container. Maintain temperature at 35° to 46°F (2° to 8°C). *Do not freeze or expose to freezing temperatures.*

Condition upon Arrival

Should not have been frozen or exposed to freezing temperatures. Refrigerate upon arrival.
If you have questions about the condition of the material at the time of delivery, you should 1) immediately place material in recommended storage; and 2) then follow your state health department immunization program policy and contact either the manufacturer's Quality Control office or the immunization program for guidance.

Storage Requirements

Refrigerate immediately upon arrival. Store at 35° to 46°F (2° to 8°C). *Do not freeze or expose to freezing temperatures.* Protect from light at all times.

Shelf Life

Check expiration date on vial or manufacturer-filled syringe.

Instructions for Use

Inspect visually for extraneous particulate matter and/or discoloration. If these conditions exist, the vaccine should not be used. Shake vial or manufacturer-filled syringe well before use. Discard vaccine if it cannot be resuspended with thorough agitation.

Shelf Life After Opening

Single-Dose Vials: The vaccine should be administered shortly after withdrawal from the vial.
Manufacturer-Filled Syringes: The vaccine should be administered shortly after the needle is attached to the syringe.

Special Instructions

Rotate stock so that the earliest dated material is used first.
Note: All vaccine materials should be disposed of using medical waste disposal procedures. Contact the state health department for details.

IPV: Inactivated Polio Vaccine

Shipping Requirements

Should be shipped in insulated container. Maintain temperature at 35° to 46°F (2° to 8°C). *Do not freeze or expose to freezing temperatures.*

Condition upon Arrival

Should not have been frozen or exposed to freezing temperatures. Refrigerate upon arrival.
If you have questions about the condition of the material at the time of delivery, you should 1) immediately place material in recommended storage; and 2) then follow your state health department immunization program policy and contact either the manufacturer's Quality Control office or the immunization program for guidance.

Storage Requirements

Refrigerate immediately upon arrival. Store at 35° to 46°F (2° to 8°C). *Do not freeze or expose to freezing temperatures.*

Shelf Life

Check expiration date on vial or manufacturer-filled syringe.

Instructions for Use

Inspect visually for extraneous particulate matter and/or discoloration. If these conditions exist, the vaccine should not be used. Shake vial or manufacturer-filled syringe well before use. Discard vaccine if it cannot be resuspended with thorough agitation.

Shelf Life After Opening

Multidose Vials: Withdraw single dose of vaccine into separate sterile needle and syringe for each immunization. The vaccine should be administered shortly after withdrawal from the vial. Unused portions of multidose vials may be refrigerated at 35° to 46°F (2° to 8°C) and used until expired, if not contaminated or unless otherwise stated in the manufacturer's product information.
Manufacturer-Filled Syringes: The vaccine should be administered shortly after the needle is attached to the syringe.

Special Instructions

Rotate stock so that the earliest dated material is used first.
Note: All vaccine materials should be disposed of using medical waste disposal procedures. Contact the state health department for details.

TIV: Trivalent Inactivated Influenza Vaccine

Shipping Requirements

Should be shipped in insulated container. Maintain temperature at 35° to 46°F (2° to 8°C). *Do not freeze or expose to freezing temperatures.*

Condition upon Arrival

Should not have been frozen or exposed to freezing temperatures. Refrigerate upon arrival.
If you have questions about the condition of the material at the time of delivery, you should 1) immediately place material in recommended storage; and 2) then follow your state health department immunization program policy and contact either the manufacturer's Quality Control office or the immunization program for guidance.

Storage Requirements

Refrigerate immediately upon arrival. Store at 35° to 46°F (2° to 8°C). *Do not freeze or expose to freezing temperatures.* Protect **Fluarix** and **FluLaval** from light at all times by storing in original package.

Shelf Life

Formulated for use during current influenza season. Check expiration date on vial or manufacturer-filled syringe.

Instructions for Use

Inspect visually for extraneous particulate matter and/or discoloration. If these conditions exist, the vaccine should not be used. Shake vial or manufacturer-filled syringe well before use. Discard vaccine if it cannot be resuspended with thorough agitation.

Shelf Life After Opening

Single-Dose Vials: The vaccine should be administered shortly after withdrawal from the vial.
Multidose Vials: Withdraw single dose of vaccine into separate sterile needle and syringe for each immunization. The vaccine should be administered shortly after withdrawal from the vial. Unused portions of multidose vials may be refrigerated at 35° to 46°F (2° to 8°C) and used until expired, if not contaminated or unless otherwise stated in the manufacturer's product information.
Manufacturer-Filled Syringes: The vaccine should be administered shortly after the needle is attached to the syringe.

Special Instructions

Rotate stock so that the earliest dated material is used first.
Note: All vaccine materials should be disposed of using medical waste disposal procedures. Contact the state health department for details.

LAIV: Live Attenuated Influenza Vaccine

Shipping Requirements

Initially shipped to authorized distributors in the frozen state 5°F (-15°C). Shipped from the distributor to healthcare facilities in the refrigerated state at 35° to 46°F (2° to 8°C).

Condition upon Arrival

Refrigerate upon arrival.

If you have questions about the condition of the material at the time of delivery, you should 1) immediately place material in recommended storage; and 2) then follow your state health department immunization program policy and contact either the manufacturer's Quality Control office or the immunization program for guidance.

Storage Requirements

Refrigerate immediately upon arrival. Store at 35° to 46°F (2° to 8°C). *Do not freeze or expose to freezing temperatures.* If LAIV is inadvertently frozen, the vaccine should be moved immediately to the refrigerator and may be used until the expiration date printed on the package.

Shelf Life

Formulated for use during current influenza season. Check expiration date on package.

Instructions for Use

LAIV is a colorless to pale yellow liquid and is clear to slightly cloudy; some particulates may be present but do not affect the use of the product. After removal of the sprayer from the refrigerator, remove the rubber tip protector. Follow manufacturer's instructions to deliver ½ dose into one nostril. Then remove the dose-divider clip and deliver the remainder of the dose into the other nostril.

Shelf Life After Opening

Single-Dose Sprayer: The vaccine should be administered shortly after removal from the refrigerator.

Special Instructions

Rotate stock so that the earliest dated material is used first.

Note: All vaccine materials should be disposed of using medical waste disposal procedures. Contact the state health department for details.

MMR: Measles, Mumps, Rubella Vaccine

Shipping Requirements

Vaccine: Should be shipped in insulated container. Must be shipped with refrigerant. Maintain temperature at 50°F (10°C) or less. If shipped with dry ice, diluent must be shipped separately.

Diluent: May be shipped with vaccine, but do not place in container with dry ice.

Condition upon Arrival

Maintain at 50°F (10°C) or less. Do not use warm vaccine. Refrigerate upon arrival.

If you have questions about the condition of the material at the time of delivery, you should 1) immediately place material in recommended storage; and 2) then follow your state health department immunization program policy and contact either the manufacturer's Quality Control office or the immunization program for guidance.

Storage Requirements

Vaccine: Refrigerate immediately upon arrival. Store at 35° to 46°F (2° to 8°C). Protect from light at all times, since such exposure may inactivate the vaccine viruses.

Diluent: May be refrigerated or stored at room temperature (68° to 77°F [20° to 25°C]). *Do not freeze or expose to freezing temperatures.*

Note: MMR vaccine may be stored in the refrigerator or freezer.

Shelf Life

Check expiration date on vial.

Instructions for Reconstitution and Use

Reconstitute just before use according to the manufacturer's instructions. Use only the diluent supplied to reconstitute the vaccine.

Shelf Life After Reconstitution, Thawing or Opening

Single-Dose Vials: After reconstitution, use immediately or store at 35° to 46°F (2° to 8°C) and protect from light. *Discard if not used within 8 hours of reconstitution.*

Multidose Vials: Withdraw single dose of reconstituted vaccine into separate sterile needle and syringe for each immunization. The vaccine should be administered shortly after withdrawal from the vial. Unused portions of multidose vials may be refrigerated at 35° to 46°F (2° to 8°C), but must be discarded if not used within 8 hours after reconstitution.

Special Instructions

Rotate stock so that the earliest dated material is used first.

Note: All vaccine materials should be disposed of using medical waste disposal procedures. Contact the state health department for details.

MCV: Meningococcal Conjugate Vaccine

Shipping Requirements

Should be shipped in insulated container. Maintain temperature at 35° to 46°F (2° to 8°C). *Do not freeze or expose to freezing temperatures.*

Condition upon Arrival

Should not have been frozen or exposed to freezing temperatures. Refrigerate upon arrival.
If you have questions about the condition of the material at the time of delivery, you should 1) immediately place material in recommended storage; and 2) then follow your state health department immunization program policy and contact either the manufacturer's Quality Control office or the immunization program for guidance.

Storage Requirements

Refrigerate immediately upon arrival. Store at 35° to 46°F (2° to 8°C). *Do not freeze or expose to freezing temperatures.*

Shelf Life

Check expiration date on vial or manufacturer-filled syringe.

Instructions for Use

Inspect visually for extraneous particulate matter and/or discoloration. If these conditions exist, the vaccine should not be used. Shake vial or manufacturer-filled syringe well before use. Discard vaccine if it cannot be resuspended with thorough agitation.

Shelf Life After Opening

Single-Dose Vials: The vaccine should be administered shortly after withdrawal from the vial.
Manufacturer-Filled Syringes: The vaccine should be administered shortly after the needle is attached to the syringe.

Special Instructions

Rotate stock so that the earliest dated material is used first.
Note: All vaccine materials should be disposed of using medical waste disposal procedures. Contact the state health department for details.

MPSV: Meningococcal Polysaccharide Vaccine

Shipping Requirements

Should be shipped in insulated container. Maintain temperature at 35° to 46°F (2° to 8°C). *Do not freeze or expose to freezing temperatures.*

Condition upon Arrival

Should not have been frozen or exposed to freezing temperatures. Refrigerate upon arrival.
If you have questions about the condition of the material at the time of delivery, you should 1) immediately place material in recommended storage; and 2) then follow your state health department immunization program policy and contact either the manufacturer's Quality Control office or the immunization program for guidance.

Storage Requirements

Vaccine: Refrigerate immediately upon arrival. Store at 35° to 46°F (2° to 8°C). *Do not freeze or expose to freezing temperatures.*
Diluent: May be refrigerated or stored at room temperature (68° to 77°F [20° to 25°C]). *Do not freeze or expose to freezing temperatures.*

Shelf Life

Check expiration date on vial.

Instructions for Reconstitution and Use

Reconstitute just before using according to the manufacturer's instructions. Use only the diluent supplied to reconstitute the vaccine.

Shelf Life After Reconstitution or Opening

Single-Dose Vials: Use within 30 minutes of reconstitution.
Multidose Vials: Unused portions of multidose vials may be refrigerated at 35° to 46°F (2° to 8°C) and used up to 35 days after reconstruction.

Special Instructions

Rotate stock so that the earliest dated material is used first.
Note: All vaccine materials should be disposed of using medical waste disposal procedures. Contact the state health department for details.

PCV: Pneumococcal Conjugate Vaccine

Shipping Requirements

Should be shipped in insulated container. Maintain temperature at 35° to 46°F (2° to 8°C). *Do not freeze or expose to freezing temperatures.*

Condition upon Arrival

Should not have been frozen or exposed to freezing temperatures. Refrigerate upon arrival.
If you have questions about the condition of the material at the time of delivery, you should 1) immediately place material in recommended storage; and 2) then follow your state health department immunization program policy and contact either the manufacturer's Quality Control office or the immunization program for guidance.

Storage Requirements

Refrigerate immediately upon arrival. Store at 35° to 46°F (2° to 8°C). *Do not freeze or expose to freezing temperatures.*

Shelf Life

Check expiration date on vial or manufacturer-filled syringe.

Instructions for Use

Inspect visually for extraneous particulate matter and/or discoloration. If these conditions exist, the vaccine should not be used. Shake vial or manufacturer-filled syringe well before use. Discard vaccine if it cannot be resuspended with thorough agitation.

Shelf Life After Opening

Single-Dose Vials: The vaccine should be administered shortly after withdrawal from the vial.
Manufacturer-Filled Syringes: The vaccine should be administered shortly after the needle is attached to the syringe.

Special Instructions

Rotate stock so that the earliest dated material is used first.
Note: All vaccine materials should be disposed of using medical waste disposal procedures. Contact the state health department for details.

PPSV: Pneumococcal Polysaccharide Vaccine

Shipping Requirements

Should be shipped in insulated container. Maintain temperature at 35° to 46°F (2° to 8°C). *Do not freeze or expose to freezing temperatures.*

Condition upon Arrival

Should not have been frozen or exposed to freezing temperatures. Refrigerate upon arrival.
If you have questions about the condition of the material at the time of delivery, you should 1) immediately place material in recommended storage; and 2) then follow your state health department immunization program policy and contact either the manufacturer's Quality Control office or the immunization program for guidance.

Storage Requirements

Refrigerate immediately upon arrival. Store at 35° to 46°F (2° to 8°C). *Do not freeze or expose to freezing temperatures.*

Shelf Life

Check expiration date on vial.

Instructions for Use

Inspect visually for extraneous particulate matter and/or discoloration. If these conditions exist, the vaccine should not be used. Shake vial or manufacturer-filled syringe well before use. Discard vaccine if it cannot be resuspended with thorough agitation.

Shelf Life After Opening

Single-Dose Vials: The vaccine should be administered shortly after withdrawal from the vial.
Multidose Syringes: Withdraw single dose of vaccine into separate sterile needle and syringe for each immunization. The vaccine should be administered shortly after withdrawal from the vial. Unused portions of multidose vials may be refrigerated at 35° to 46°F (2° to 8°C) and used until expired, if not contaminated or unless otherwise stated in the manufacturer's product information.

Special Instructions

Rotate stock so that the earliest dated material is used first.
Note: All vaccine materials should be disposed of using medical waste disposal procedures. Contact the state health department for details.

Rotavirus Vaccine

Shipping Requirements

Should be shipped in insulated container. Maintain temperature at 35° to 46°F (2° to 8°C). *Do not freeze or expose to freezing temperatures.*

Condition upon Arrival

Should not have been frozen or exposed to freezing temperatures. Refrigerate upon arrival.
If you have questions about the condition of the material at the time of delivery, you should 1) immediately place material in recommended storage; and 2) then follow your state health department immunization program policy and contact either the manufacturer's Quality Control office or the immunization program for guidance.

Storage Requirements

Refrigerate immediately upon arrival. Store at 35° to 46°F (2° to 8°C). *Do not freeze or expose to freezing temperatures.* Protect from light at all times, since such exposure may inactivate the vaccine viruses.

Shelf Life

Check expiration date on package.

Instructions for Reconstitution or Use

Each dose of **RotaTeq** is supplied in a container consisting of a squeezable plastic, latex-free dosing tube with a twist-off cap, allowing for direct oral administration. The dosing tube is contained in a pouch. Remove the dosing tube from the pouch, screw the cap clockwise to puncture the tube, and screw the cap off counter-clockwise so that the liquid can be squeezed from the tube during oral administration of the vaccine.
Each dose of **Rotarix** is supplied as a vial of lyophilized vaccine. The 1mL of diluent is supplied in a prefilled oral applicator with a plunger stopper (contains latex), and a transfer adapter for reconstitution.

Shelf Life After Opening

Pouched Single-Dose Tubes: RoteTeq vaccine should be administered shortly after withdrawal from the refrigerator. The dosing tube should not be returned to the refrigerator once the screw cap has been removed.
Oral Applicator: Rotarix should be administered within 24 hours of reconstitution.

Special Instructions

Rotate stock so that the earliest dated material is used first.
Note: All vaccine materials should be disposed of using medical waste disposal procedures. Contact the state health department for details.

Varicella (Chickenpox) Vaccine

Shipping Requirements

Vaccine: Should be shipped in insulated container. Must be shipped with dry ice only, at 5°F (-15°C) or colder. Should be delivered within 2 days.

Diluent: May be shipped with vaccine, but do not place in container with dry ice.

Condition upon Arrival

Should be frozen. Vaccine should remain at 5°F (-15°C) or colder until arrival at the healthcare facility. Dry ice should still be present in the shipping container when the vaccine is delivered.

If you have questions about the condition of the material at the time of delivery, you should 1) immediately place material in recommended storage; and 2) then follow your state health department immunization program policy and contact either the manufacturer's Quality Control office or the immunization program for guidance.

Storage Requirements

Vaccine: Freeze immediately upon arrival. Maintain vaccine in a continuously frozen state at 5°F (-15°C) or colder. *No freeze/thaw cycles are allowed with this vaccine.* Vaccine should only be stored in freezers or refrigerator/freezers with separate external doors and compartments. Acceptable storage may be achieved in standard household freezers purchased in the last 10 years, and standard household refrigerator/freezers a separate, sealed freezer compartment. "Dormitory-style" units are not appropriate for the storage of varicella vaccine. *Do not store lyophilized vaccine in the refrigerator.* If lyophilized vaccine is inadvertently stored in the refrigerator, it should be used within 72 hours. Lyophilized vaccine stored at 35° to 46° F (2° to 8°C) which is not used within 72 hours should be discarded. Protect the vaccine from light at all times since such exposure may inactivate the vaccine virus.

In order to maintain temperatures of 5°F (-15°C) or colder, it will be necessary in most refrigerator/freezer models to turn the temperature dial down to the coldest setting. This may result in the refrigerator compartment temperature being lowered as well. Careful monitoring of the refrigerator temperature will be necessary to avoid freezing killed or inactivated vaccines.

Diluent: May be refrigerated or stored at room temperature (68° to 77°F [20° to 25°C]). *Do not freeze or expose to freezing temperatures.*

Shelf Life

Check expiration date on vial.

Instructions for Reconstitution and Use

Reconstitute just before use according to the manufacturer's instructions. Use only the diluent supplied to reconstitute the vaccine.

Shelf Life After Reconstitution, Thawing or Opening

Single-Dose Vials: Discard reconstituted vaccine if it is not used within *30 minutes* of reconstitution. *Do not freeze reconstituted vaccine.*

Special Instructions

Rotate stock so that the earliest dated material is used first.

If this vaccine is stored at a temperature warmer than 5°F (-15°C), it will result in a loss of potency and a reduced shelf life. If a power outage or some other situation occurs that results in the vaccine storage temperature rising above the recommended temperature, the healthcare provider should contact Merck, the vaccine manufacturer, at 1-800-9-VARIVAX for an evaluation of the product potency before using the vaccine.

Note: All vaccine materials should be disposed of using medical waste disposal procedures. Contact the state health department for details.

Zoster (Shingles) Vaccine

Shipping Requirements

Vaccine: Should be shipped in insulated container. Must be shipped with dry ice only, at 5°F (-15°C) or colder. Should be delivered within 2 days.
Diluent: May be shipped with vaccine, but do not place in container with dry ice.

Condition upon Arrival

Should be frozen. Vaccine should remain at 5°F (-15°C) or colder until arrival at the healthcare facility. Dry ice should still be present in the shipping container when the vaccine is delivered.
If you have questions about the condition of the material at the time of delivery, you should 1) immediately place material in recommended storage; and 2) then follow your state health department immunization program policy and contact either the manufacturer's Quality Control office or the immunization program for guidance.

Storage Requirements

Vaccine: Freeze immediately upon arrival. Maintain vaccine in a continuously frozen state at 5°F (-15°C) or colder. *No freeze/thaw cycles are allowed with this vaccine.* Vaccine should only be stored in freezers or refrigerator/freezers with separate external doors and compartments. Acceptable storage may be achieved in standard household freezers purchased in the last 10 years, and standard household refrigerator/freezers a separate, sealed freezer compartment. "Dormitory-style" units are not appropriate for the storage of varicella vaccine. *Do not store lyophilized vaccine in the refrigerator.* Protect the vaccine from light at all times since such exposure may inactivate the vaccine virus.
In order to maintain temperatures of 5°F (-15°C) or colder, it will be necessary in most refrigerator/freezer models to turn the temperature dial down to the coldest setting. This may result in the refrigerator compartment temperature being lowered as well. Careful monitoring of the refrigerator temperature will be necessary to avoid freezing killed or inactivated vaccines.
Diluent: May be refrigerated or stored at room temperature (68° to 77°F [20° to 25°C]). *Do not freeze or expose to freezing temperatures.*

Shelf Life

Check expiration date on vial.

Instructions for Reconstitution and Use

Reconstitute just before use according to the manufacturer's instructions. Use only the diluent supplied to reconstitute the vaccine.

Shelf Life After Reconstitution, Thawing or Opening

Single-Dose Vials: Discard reconstituted vaccine if it is not used within *30 minutes* of reconstitution. *Do not freeze reconstituted vaccine.*

Special Instructions

Rotate stock so that the earliest dated material is used first.
If this vaccine is stored at a temperature warmer than 5°F (-15°C), it will result in a loss of potency and a reduced shelf life. If a power outage or some other situation occurs that results in the vaccine storage temperature rising above the recommended temperature, the healthcare provider should contact Merck, the vaccine manufacturer, at 1-800-MERCK-90 for an evaluation of the product potency before using the vaccine.
Note: All vaccine materials should be disposed of using medical waste disposal procedures. Contact the state health department for details.

Manufacturer Quality Control Office Telephone Numbers

Manufacturer/Distributor	Telephone Number	Product(s)
sanofi pasteur www.sanofipasteur.us	800-822-2463	DTaP, DTaP-Hib, DT, DTaP-IPV-Hib, Td, Tdap, TT, Hib, Influenza (TIV), IPV, MCV, MPSV
Talecris Biotherapeutics www.telecrisusa.com	800-520-2807	HBIG, IGIM, RIG, TIG
Centers for Disease Control & Prevention Drug Service www.cdc.gov/ncidod.srp/drugs/drug-service.html	404-639-3670	Distributor for Diphtheria antitoxin
Novartis www.novartis-vaccines.com/products/index/shtml	800-244-7668	Influenza (TIV)
GlaxoSmithKline www.gsk.com	866-475-8222 (customer support) 888-825-5249 (customer support)	DTaP, DTaP-IPV, DTaP-HepB-IPV, Tdap, HepA, HepB, HepA-HepB, Rotavirus, Influenza (TIV)
Massachusetts Biological Labs	617-474-3000 617-983-6400	Td, IGIM, TT
MedImmune, Inc. www.medimmune.com	877-633-4411	Influenza (LAIV)
Merck www.merckvaccines.com	800-637-2590	Hib, Hib-HepB, HepA, HepB, HPV, MMR, PPSV, Rotavirus, Varicella, Zoster
Nabi Biopharmaceuticals www.nabi.com	800-635-1766	HBIG
Wyeth www.wyeth.com	800-934-5556	Hib, PCV

April 2009

Checklist for Safe Vaccine Handling and Storage

Here are the 20 most important things you can do to safeguard your vaccine supply. Are you doing them all? Reviewing this list can help you improve your clinic's vaccine management practices.

Yes	No		
_____	_____	1.	We have a designated person in charge of the handling and storage of our vaccines.
_____	_____	2.	We have a back-up person in charge of the handling and storage of our vaccines.
_____	_____	3.	A vaccine inventory log is maintained that documents: _____ Vaccine name and number of doses received _____ Date the vaccine was received _____ Arrival condition of vaccine _____ Vaccine manufacturer and lot number _____ Vaccine expiration date
_____	_____	4.	Our refrigerator for vaccines is either household-style or commercial-style, NOT dormitory-style. The freezer compartment has a separate exterior door. Alternatively, we use two storage units: a free-standing refrigerator and a separate, free-standing freezer.
_____	_____	5.	We do NOT store any food or drink in the refrigerator or freezer.
_____	_____	6.	We store vaccines in the middle of the refrigerator or freezer, and NOT in the door.
_____	_____	7.	We stock and rotate our vaccine supply so that the newest vaccine of each type (with the longest expiration date) is placed behind the vaccine with the shortest expiration date.
_____	_____	8.	We check vaccine expiration dates and we first use those that will expire soonest.
_____	_____	9.	We post a sign on the refrigerator door showing which vaccines should be stored in the refrigerator and which should be stored in the freezer.
_____	_____	10.	We always keep a thermometer in the refrigerator.
_____	_____	11.	The temperature in the refrigerator is maintained at 35–46°F (2–8°C).
_____	_____	12.	We keep extra containers of water in the refrigerator to help maintain cold temperatures.
_____	_____	13.	We always keep a thermometer in the freezer.
_____	_____	14.	The temperature in the freezer is maintained at +5°F (-15°C) or colder.
_____	_____	15.	We keep ice packs and other ice-filled containers in the freezer to help maintain cold temperatures.
_____	_____	16.	We post a temperature log on the refrigerator door on which we record the refrigerator and freezer temperatures twice a day—first thing in the morning and at clinic closing time—and we know whom to call if the temperature goes out of range.
_____	_____	17.	We have a "Do Not Unplug" sign next to the refrigerator's electrical outlet.
_____	_____	18.	In the event of a refrigerator failure, we take the following steps: _____ We assure that the vaccines are placed in a location with adequate refrigeration. _____ We mark exposed vaccines and separate them from undamaged vaccines. _____ We note the refrigerator or freezer temperature and contact the vaccine manufacturer or state health department to determine how to handle the affected vaccines. _____ We follow the vaccine manufacturer's or health department's instructions as to whether the affected vaccines can be used, and, if so, we mark the vials with the revised expiration date provided by the manufacturer or health department.
_____	_____	19.	We have obtained a detailed written policy for general and emergency vaccine management from our local or state health department.
_____	_____	20.	If all above answers are "yes," we are patting ourselves on the back. If not, we have assigned someone to implement needed changes!

Technical content reviewed by the Centers for Disease Control and Prevention, July 2008.

www.immunize.org/catg.d/p3035.pdf • Item #P3035 (7/08)

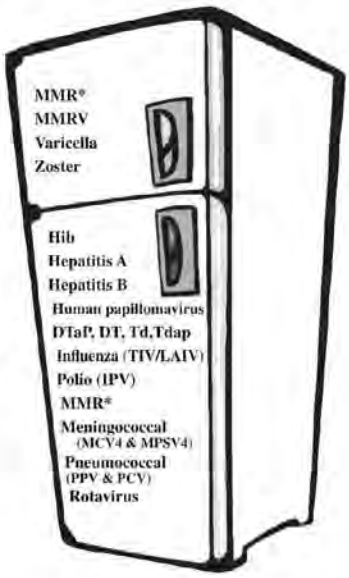
Immunization Action Coalition • 1573 Selby Ave. • St. Paul, MN 55104 • (651) 647-9009 • www.immunize.org • www.vaccineinformation.org

Vaccine Handling Tips

Outdated or improperly stored vaccines won't protect patients!

Maintain freezer temperature at 5°F (-15°C) or colder →

Maintain refrigerator temperature at 35–46°F (2–8°C) →



Order vaccine carefully.
Inventory your vaccine at least monthly and before placing an order. Expired vaccine must never be used and is money wasted!

Store vaccine correctly.†
Refrigerate or freeze immediately upon receiving shipment. Do not store vaccine in the door of the refrigerator or freezer. Inactivated vaccines should always be placed in the middle of the refrigerator far enough away from the freezer compartment to protect them from freezing.

Always use the vaccine with the earliest expiration date first.
Move vaccine with the earliest expiration date to the front and mark it to be used first. Keep vials in their boxes. Never use outdated vaccine.

Stabilize temperatures.
Store ice packs in the freezer and large jugs of water in the refrigerator along with the vaccine. This will help maintain a stable, cold temperature in case of a power failure or if the refrigerator or freezer doors are opened frequently or left open. Frequent opening of the refrigerator unit's doors can lead to temperature variations inside, which could affect vaccine efficacy. For this reason you should not store food or beverages in the refrigerator or freezer.

Safeguard the electrical supply to the refrigerator.
Make sure the refrigerator is plugged into an outlet in a protected area where it cannot be disconnected accidentally. Label the refrigerator, electrical outlets, fuses, and circuit breakers on the power circuit with information that clearly identifies the perishable nature of vaccines and the immediate steps to be taken in case of interruption of power (use DO NOT UNPLUG stickers). If your building has auxiliary power, use the outlet supplied by that system.

*MMR may be stored in either the freezer or the refrigerator.

†Refer to package insert for specific instructions on the storage of each vaccine. If you have questions about the condition of the vaccine, you should immediately place the vaccine in recommended storage and call the vaccine manufacturer(s) to determine whether the potency of the vaccine(s) has been affected. For other questions, call the immunization program at your state or local health department.

Record your health department's phone number here: _____

Adapted by the Immunization Action Coalition, courtesy of the Minnesota Department of Health

Technical content reviewed by the Centers for Disease Control and Prevention, May 2007.

www.immunize.org/catg.d/p3048.pdf • Item #P3048 (5/07)

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WARNING

Do not unplug the refrigerator/
freezer or break circuit.
Expensive vaccine in storage.



In event of electrical problem, immediately contact:

WARNING

Do not unplug the refrigerator/
freezer or break circuit.
Expensive vaccine in storage.



In event of electrical problem, immediately contact:

WARNING

Do not unplug the refrigerator/
freezer or break circuit.
Expensive vaccine in storage.



In event of electrical problem, immediately contact:

APPENDIX D
Vaccine Administration

"Vaccine Administration" Guidelines D-1

Skills Checklist for Immunization D-16

Immunization Site Maps D-18

"Comforting Restraint" for Immunizations D-23

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Medical Management of Vaccine Reactions (Children & Teens) D-28

Medical Management of Vaccine Reactions (Adults). D-30

Appendix D

Vaccine Administration

Appropriate vaccine administration is critical to vaccine effectiveness. The recommended site, route and dosage for each vaccine are based on clinical trials, practical experience and theoretical considerations. The following information provides general guidelines for administration of vaccines for those who administer vaccines, as well as those in training, education and supervisory positions. This information should be used in conjunction with professional standards for medication administration, vaccine manufacturers' product guidelines, CDC's Advisory Committee on Immunization Practices (ACIP) General Recommendations on Immunization, the American Academy of Pediatrics' (AAP) Report of the Committee on Infectious Diseases *Red Book*, and state/agency-related policies and procedures. An education plan that includes competency-based training on vaccine administration should be considered for all persons who administer vaccines to children or adults (refer to "Skills Checklist for Immunization" - page D16).

Preparation

Patient Preparation - Patients should be prepared for vaccination with consideration for their age and stage of development. Parents/guardians and patients should be encouraged to take an active role before, during and after the administration of vaccines (see "Be There for Your Child During Shots" poster at http://cdlhn.com/default.htm, search for IMM674S).

- **Screening** - All patients should be screened for contraindications and precautions for each scheduled vaccine. Many state immunization programs and other organizations have developed and make available standardized screening tools. Basic screening questions can be found in Chapter 2. Sample screening forms for children and adults are available from the Immunization Action Coalition (www.immunize.org).

- **Vaccine Safety & Risk Communication** - Parents/guardians and patients are exposed through the media to information about vaccines, some of which is inaccurate or misleading. Healthcare providers should be prepared to discuss the benefits and risks of vaccines using Vaccine Information Statements (VIS) and other reliable resources. Establishing an open dialogue provides a safe, trust-building environment in which individuals can freely evaluate information, discuss vaccine concerns and make informed decisions regarding immunization (see Chapter 4 and Appendices E and F).

- **Atraumatic Care** - Vaccine safety issues and the need for multiple injections have increased the concerns and anxiety associated with immunizations. Healthcare providers need to display confidence and establish an environment that promotes a sense of security and trust for the patient and family, utilizing a variety of techniques to minimize the stress and discomfort associated with receiving injections. This is particularly important when administering vaccines to children.

  - **Positioning & Comforting Restraint** - The healthcare provider must accommodate for the patient's comfort, safety, age, activity level, and the site of administration when considering patient positioning and restraint. For a child, the parent/guardian should be encouraged to hold the child during administration. If the parent is uncomfortable, another person may assist or the patient may be

positioned safely on an examination table (refer to "Comforting Restraint for Immunizations" - page D23).

- **Pain Control** - Pain is a subjective phenomenon influenced by multiple factors, including an individual's age, anxiety level, previous healthcare experiences, and culture. Consideration for these factors is important as the provider develops a planned approach to management of injection pain (see “Be There for Your Child During Shots” poster).

  - *Topical Anesthetics* or a vapocoolant spray may be applied to decrease pain at the injection site. These products should be used only for the ages recommended and as directed by the product manufacturer.

  - *Analgesic Agents* - A non-aspirin containing pain reliever may be considered to decrease discomfort and fever following vaccination. These products should be used only in age-appropriate doses.

  - *Diversionary Techniques* - Age-appropriate non pharmacologic techniques may provide distraction from pain associated with injections. Diversion can be accomplished through a variety of techniques, some of which are outlined on the “Be There for Your Child During Shots” poster.

  - *Dual Administrators* - Some providers favor the technique of two individuals simultaneously administering vaccines at separate sites. The premise is that this procedure may decrease anxiety from anticipation of the next injection(s). The effectiveness of this procedure in decreasing pain or stress associated with vaccine injections has not been evaluated.

Infection Control - Healthcare providers should follow Standard Precautions to minimize the risks of spreading disease during vaccine administration.

- **Handwashing** - The single, most effective disease prevention activity is good handwashing. Hands should be washed thoroughly with soap and water or cleansed with an alcohol-based waterless antiseptic between patients, before vaccine preparation or any time hands become soiled, e.g. diapering, cleaning excreta.

- **Gloving** - Gloves are not required to be worn when administering vaccines unless the person administering the vaccine is likely to come into contact with potentially infectious body fluids or has open lesions on the hands. It is important to remember that gloves cannot prevent needlestick injuries.

- **Needlestick Injuries** should be reported immediately to the site supervisor, with appropriate care and follow-up given as directed by state/local guidelines. Safety needles or needle-free injection devices should be used if available to reduce the risk of injury.

- **Equipment Disposal** - Used needles should not be detached from syringes, recapped or cut before disposal. All used syringe/needle devices should be placed in puncture proof containers to prevent accidental needlesticks and reuse. Empty or expired vaccine vials are considered medical waste and

should be disposed of according to state regulations.

Vaccine Preparation - Proper vaccine handling and preparation is critical in maintaining the integrity of the vaccine during transfer from the manufacturer's vial to the syringe and ultimately to the patient.

- **Equipment Selection**

  - **Syringe Selection** - A separate needle and syringe should be used for each injection. A parenteral vaccine may be delivered in either a 1-mL or 3-mL syringe as long as the prescribed dosage is delivered. Syringe devices with sharps engineered sharps injury protection are availble, recommended by OSHA, and required in many states to reduce the incidence of needle stick injuries and potential disease transmission. Personnel should be involved in evaluation and selection of these products. Staff should receive training with these device before using them in the clinical area.

  - **Needle Selection** - Vaccine must reach the desired tissue site for optimal immune response. Therefore, needle selection should be based upon the prescribed route, size of the individual, volume and viscosity of the vaccine, and injection technique. (See Subcutaneous & Intramuscular Injections, below.) Typically, vaccines are not highly viscous, and therefore a fine gauge needle (22-25 gauge) can be used.

  - **Needle-Free Injection** - A new generation of needle-free vaccine delivery devices has been developed in an effort to decrease the risks of needlestick injuries to healthcare workers and to prevent improper reuse of syringes and needles. For more information on needle-free injection technology, see the CDC website: www.cdc.gov/od/science/iso/vaxtech/nfit/.

- **Inspecting Vaccine** - Each vaccine vial should be carefully inspected for damage or contami nation prior to use. The expiration date printed on the vial or box should be checked. Vaccine can be used through the last day of the month indicated by the expiration date unless otherwise stated on the package labeling. Expired vaccine should never be used.

- **Reconstitution** - Some vaccines are prepared in a lyophilized form that requires reconstitution, which should be done according to manufacturer guidelines. Diluent solutions vary; use only the specific diluent supplied for the vaccine. Once reconstituted, the vaccine must be either administered within the time guidelines provided by the manufacturer or discarded. Changing the needle after reconstitution of the vaccine is not necessary unless the needle has become contaminated or bent. Continue with standard medication preparation guidelines.

- **Prefilling Syringes** - CDC strongly discourages filling syringes in advance, because of the increased risk of administration errors. Once the vaccine is in the syringe it is difficult to identify the type or brand of vaccine. Other problems associated with this practice are vaccine wastage, and possible bacterial growth in vaccines that do not contain a preservative. Furthermore, medication administration guidelines state that the individual who administers a medication should be the one to draw up and prepare it. An alternative to prefilling syringes is to use filled syringes supplied by the vaccine manufacturer. Syringes other than those filled by the manufacturer are designed for immediate

administration, not for vaccine storage.

In certain circumstances, such as a large influenza clinic, more than one syringe can be filled. One person should prefill only a few syringes at a time, and the same person should administer them. Any syringes left at the end of the clinic day should be discarded.

Under no circumstances should MMR, varicella, or zoster vaccines ever be reconstituted and drawn prior to the immediate need for them. These live virus vaccines are unstable and begin to deteriorate as soon as they are reconstituted with diluent.

- **Labeling** - Once a vaccine is drawn into a syringe, the content should be indicated on the syringe. There are a variety of methods for identifying or labeling syringes (e.g. keep syringes with the appropriate vaccine vials, place the syringes in a labeled partitioned tray, or use color coded labels or preprinted labels).

Strategies to Prevent Immunization Administration Errors

1. When possible, involve staff in the selection of vaccine products to be used in your facility. Orient new staff to vaccines your office uses and validate their knowledge and skills about vaccine administration. Train all staff on the use and administration of new vaccines.

2. Keep current reference materials available for staff on each vaccine used in your facility. Keep reference sheets for timing and spacing, recommended sites, routes, and needle lengths posted for easy reference in your medication preparation area.

3. Rotate vaccines so that those with the shortest expiration dates are in the front of the storage unit. Use these first and frequently check the storage unit to remove and discard any expired vaccine.

4. Consider the potential for product mix-ups when storing vaccines. Do not store sound-alike and look-alike vaccines next to each other. Label storage containers or baskets with the age indications for each vaccine.

5. Administer only vaccines that you have prepared for administration. Triple-check your work before you administer a vaccine and ask other staff to do the same.

6. Counsel parents and patients on vaccines to be administered and the importance of maintaining immunization records on all family members. Educated clients may notice a potential error and help prevent it.

Administering Vaccines: Dose, Route, Site, and Needle Size

Vaccines	Dose	Route
Diphtheria, Tetanus, Pertussis (DTaP, DT, Tdap, Td)	0.5 mL	IM
***Haemophilus influenzae* type b (Hib)**	0.5 mL	IM
Hepatitis A (HepA)	≤18 yrs: 0.5 mL ≥19 yrs: 1.0 mL	IM
Hepatitis B (HepB) **Persons 11–15 yrs may be given Recombivax HB® (Merck) 1.0 mL adult formulation on a 2-dose schedule*	≤19 yrs: 0.5 mL* ≥20 yrs: 1.0 mL	IM
Human papillomavirus (HPV)	0.5 mL	IM
Influenza, live attenuated (LAIV)	0.2 mL	Intranasal spray
Influenza, trivalent inactivated (TIV)	6–35 mos: 0.25 mL ≥3 yrs: 0.5 mL	IM
Measles, mumps, rubella (MMR)	0.5 mL	SC
Meningococcal – conjugate (MCV)	0.5 mL	IM
Meningococcal – polysaccharide (MPSV)	0.5 mL	SC
Pneumococcal conjugate (PCV)	0.5 mL	IM
Pneumococcal polysaccharide (PPSV)	0.5 mL	IM or SC
Polio, inactivated (IPV)	0.5 mL	IM or SC
Rotavirus (RV)	2.0 mL	Oral
Varicella (Var)	0.5 mL	SC
Zoster (Zos)	0.65 mL	SC
Combination Vaccines		
DTaP+HepB+IPV (Pediarix®) **DTaP+Hib+IPV (Pentacel®)** **DTaP+Hib (Trihibit®)** **DTaP+IPV (Kinrix®)** **Hib+HepB (Comvax®)**	0.5 mL	IM
MMR+Var (ProQuad®)	≤12 yrs: 0.5 mL	SC
HepA+HepB (Twinrix®)	≥18 yrs: 1.0 mL	IM

Injection Site and Needle Size

Subcutaneous (SC) injection

Use a 23–25 gauge needle. Choose the injection site that is appropriate to the person's age and body mass.

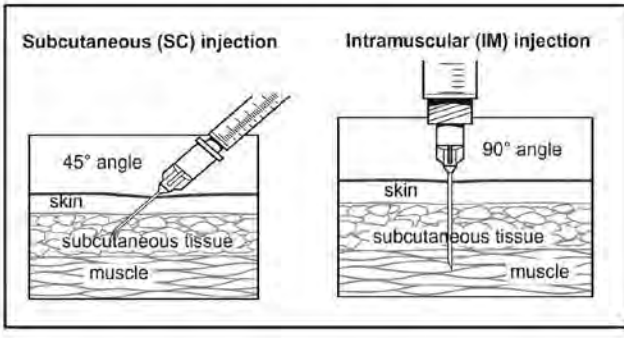
Age	Needle Length	Injection Site
Infants (1–12 mos)	⅝"	Fatty tissue over anterolateral thigh muscle
Children 12 mos or older, adolescents, and adults	⅝"	Fatty tissue over anterolateral thigh muscle or fatty tissue over triceps

Intramuscular (IM) injection

Use a 22–25 gauge needle. Choose the injection site and needle length appropriate to the person's age and body mass.

Age	Needle Length	Injection Site
Newborns (1st 28 days)	⅝"*	Anterolateral thigh muscle
Infants (1–12 mos)	1"	Anterolateral thigh muscle
Toddlers (1–2 yrs)	1–1¼" ⅝–1"*	Anterolateral thigh muscle or deltoid muscle of arm
Children & teens (3–18 years)	⅝–1"* 1"–1¼"	Deltoid muscle of arm or anterolateral thigh muscle
Adults 19 yrs or older		
Male or female less than 130 lbs	⅝–1"*	Deltoid muscle of arm
Female 130–200 lbs Male 130–260 lbs	1–1½"	Deltoid muscle of arm
Female 200+ lbs Male 260+ lbs	1½"	Deltoid muscle of arm

**A ⅝" needle may be used only if the skin is stretched tight, subcutaneous tissue is not bunched, and injection is made at a 90-degree angle.*



Please note: Always refer to the package insert included with each biologic for complete vaccine administration information. CDC's Advisory Committee on Immunization Practices (ACIP) recommendations for the particular vaccine should be reviewed as well.

Technical content reviewed by the Centers for Disease Control and Prevention, February 2009

www.immunize.org/catg.d/p3085.pdf • Item #P3085 (2/09)

Administering Vaccines to Adults: Dose, Route, Site, Needle Size, and Preparation

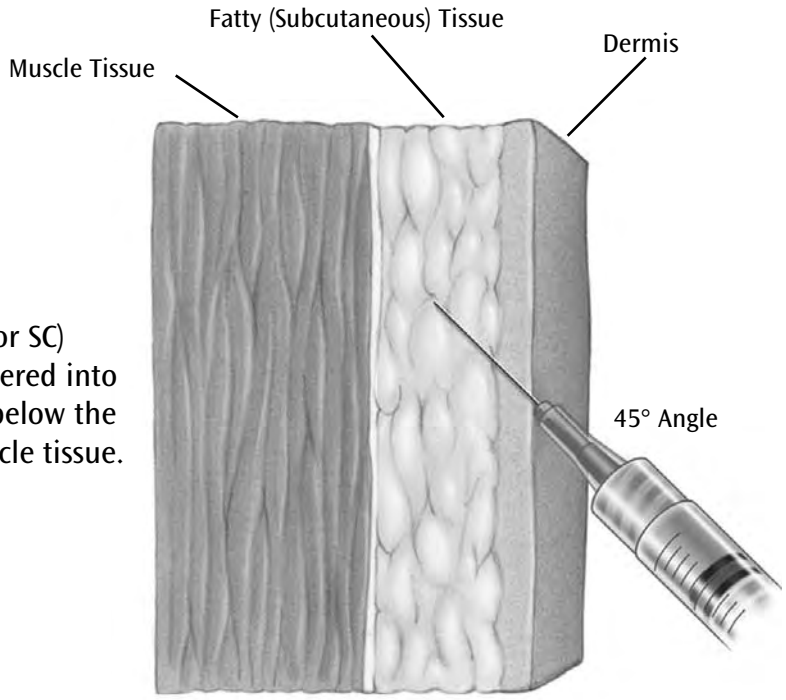
Vaccine	Dose	Route	Site	Needle Size	Vaccine Preparation
Tetanus, Diphtheria (Td) with Pertussis (Tdap)	0.5 mL	IM	Deltoid muscle	22–25g, 1–1½"*	Shake vial vigorously to obtain a uniform suspension prior to withdrawing each dose. Whenever solution and container permit, inspect vaccine visually for particulate matter and/or discoloration prior to administration. If problems are noted (e.g., vaccine cannot be resuspended), the vaccine should not be administered.
Hepatitis A (HepA)	≤18 yrs.: 0.5 mL ≥19 yrs.: 1.0 mL	IM	Deltoid muscle	22–25g, 1–1½"*	
Hepatitis B (HepB)	≤19 yrs.: 0.5 mL ≥20 yrs.: 1.0 mL	IM	Deltoid muscle	22–25g, 1–1½"*	
HepA+HepB (Twinrix)	≥18 yrs.: 1.0 mL	IM	Deltoid muscle	22–25g, 1–1½"*	
Human papillomavirus (HPV)	0.5 mL	IM	Deltoid muscle	22–25g, 1–1½"*	
Influenza, trivalent inactivated (TIV)	0.5 mL	IM	Deltoid muscle	22–25g, 1–1½"*	
Pneumococcal polysaccharide (PPSV)	0.5 mL	IM	Deltoid muscle	22–25g, 1–1½"*	
		SC	Fatty tissue over triceps	23–25g, ⅝"	
Meningococcal, conjugated (MCV)	0.5 mL	IM	Deltoid muscle	22–25g, 1–1½"*	
Meningococcal, polysaccharide (MPSV)	0.5 mL	SC	Fatty tissue over triceps	23–25g, ⅝"	Reconstitute just before using. Use only the diluent supplied with the vaccine. Inject the volume of the diluent shown on the diluent label into the vial of lyophilized vaccine and gently agitate to mix thoroughly. Withdraw the entire contents and administer immediately after reconstitution. Discard single dose MPSV, varicella, and zoster vaccines if not used within 30 minutes after reconstitution. **Note:** Unused reconstituted MMR vaccine and multidose MPSV vaccine may be stored at 35–46°F (2–8°C) for a limited time. The reconstituted MPSV vaccine must be used within 35 days; the reconstituted MMR vaccine must be used within 8 hours. Do not freeze either reconstituted vaccine.
Measles, mumps, rubella (MMR)	0.5 mL	SC	Fatty tissue over triceps	23–25g, ⅝"	
Zoster (Zos)	0.65 mL	SC	Fatty tissue over triceps	23–25g, ⅝"	
Varicella (Var)	0.5 mL	SC	Fatty tissue over triceps	23–25g, ⅝"	
Influenza, live, attenuated (LAIV)	0.2 mL (0.1 mL into each nostril)	Intranasal spray	Intranasal	NA	Consult package insert.

*When giving intramuscular injections, a ⅝" needle is sufficient in adults weighing <130 lbs (<60 kg); a 1" needle is sufficient in adults weighing 130–152 lbs (60–70 kg); a 1–1½" needle is recommended in women weighing 152–200 lbs (70–90 kg) and men weighing 152–260 lbs (70–118 kg); a 1½" needle is recommended in women weighing >200 lbs (>90 kg) or men weighing >260 lbs (>118 kg). A ⅝" (16mm) needle may be used only if the skin is stretched tight, the subcutaneous tissue is not bunched, and injection is made at a 90-degree angle.

Please note: Always refer to the package insert included with each biologic for complete vaccine administration information. CDC's Advisory Committee on Immunization Practices (ACIP) recommendations for the particular vaccine should be reviewed as well. Access the ACIP recommendations at www.immunize.org/acip.

Technical content reviewed by the Centers for Disease Control and Prevention, February 2009

www.immunize.org/catg.d/p3084.pdf • Item #P3084 (2/09)



Lynne Larson, www.biovisuals.com

- **Subcutaneous** (Sub-Q or SC) injections are administered into the fatty tissue found below the dermis and above muscle tissue.

- **Site** - Subcutaneous tissue can be found all over the body. The usual sites for vaccine administration are the thigh (for infants <12 months of age) and the upper outer triceps of the arm (for persons ≥12 months of age). If necessary, the upper outer triceps area can be used to administer subcutaneous injections to infants.




Lynne Larson, www.biovisuals.com

- **Needle Gauge & Length** - 5/8-inch, 23- to 25-gauge needle

- **Technique**

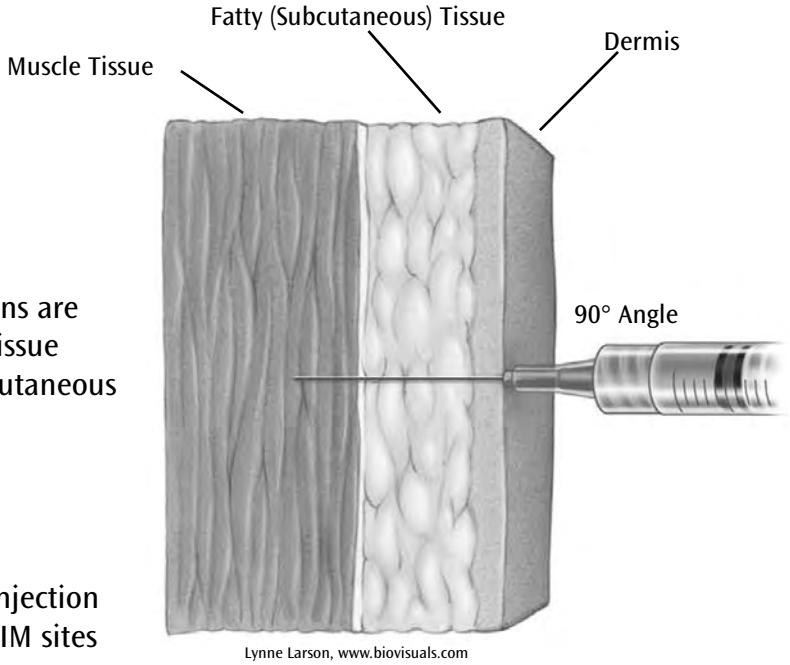
  - Follow standard medication administration guidelines for site assessment/selection and site preparation.

  - To avoid reaching the muscle, pinch up the fatty tissue, insert the needle at a 45° angle and inject the vaccine into the tissue.

  - Withdraw the needle and apply light pressure to the injection site for several seconds with a dry cotton ball or gauze.



Subcutaneous Administration Techniques



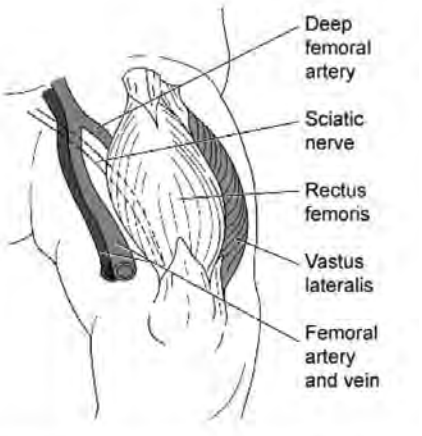
Lynne Larson, www.biovisuals.com

- **Intramuscular** (IM) injections are administered into muscle tissue below the dermis and subcutaneous tissue.

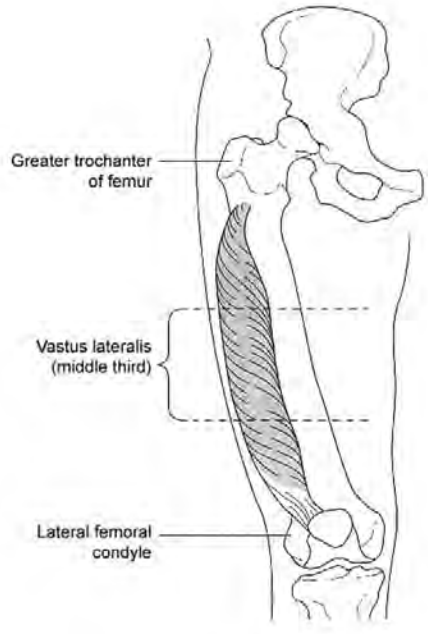
- **Site** - Although there are several IM injection sites on the body, the recommended IM sites for vaccine administration are the vastus lateralis muscle (anterolateral thigh) and the deltoid muscle (upper arm). The site depends on the age of the individual and the degree of muscle development.



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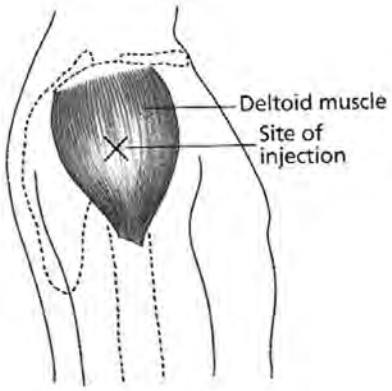
The vastus lateralis muscle of the upper thigh used for intramuscular injections.



The vastus lateralis site of the right thigh, used for an intramuscular injection.



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- **Needle Gauge** - 22- to 25-gauge needle

- **Needle Length** - For all intramuscular injections, the needle should be long enough to reach the muscle mass and prevent vaccine from seeping into subcutaneous tissue, but not so long as to involve underlying nerves, blood vessels, or bone. The vaccinator should be familiar with the anatomy of the area into which the vaccine will be injected.

  Decision on needle size and site of injection must be made for each person on the basis of the size of the muscle, the thickness of adipose tissue at the injection site, the volume of the material to be administered, injection technique, and the depth below the muscle surface into which the material is to be injected

  - *Infants (Younger Than 12 Months)*
    For the majority of infants, the anterolateral aspect of the thigh is the recommended site for injection because it provides a large muscle mass. The muscles of the buttock have not been used for administration of vaccines in infants and children because of concern about potential injury to the sciatic nerve, which is well documented after injection of antimicrobial agents into the buttock. If the gluteal muscle must be used, care should be taken to define the anatomic landmarks.*

*If the gluteal muscle is chosen, injection should be administered lateral and superior to a line between the posterior superior iliac spine and the greater trochanter or in the ventrogluteal site, the center of a triangle bounded by the anterior superior iliac spine, the tubercle of the iliac crest, and the upper border of the greater trochanter.

Injection technique is the most important factor to ensure efficient intramuscular vaccine delivery. If the subcutaneous and muscle tissue are bunched to minimize the chance of striking bone, a 1-inch needle is required to ensure intramuscular administration in infants. For the majority of infants, a 1-inch, 22-25-gauge needle is sufficient to penetrate muscle in an infant's thigh. For new born (first 28 days of life) and premature infants, a 5/8 inch needle usually is adequate if the skin is stretched flat between thumb and forefinger and the needle inserted at a 90-degree angle to the skin.

- *Toddlers and Older Children (12 Months through 10 Years)*
  The deltoid muscle should be used if the muscle mass is adequate. The needle size for deltoid site injections can range from 22 to 25 gauge and from 5/8 to 1 inch on the basis of the size of the muscle and the thickness of adipose tissue at the injection site. A 5/8-inch needle is adequate only for the deltoid muscle and only if the skin is stretched flat between thumb and forefinger and the needle inserted at a 90° angle to the skin. For toddlers, the anterolateral thigh can be used, but the needle should be at least 1 inch in length.

- *Adolescents and Adults (11 Years or Older)*
  For adults and adolescents, the deltoid muscle is recommended for routine intramuscular vaccinations. The anterolateral thigh also can be used. For men and women weighing less than 130 lbs (60 kg) a 5/8-1-inch needle is sufficient to ensure intramuscular injection. For women weighing 130-200 lbs (60-90 kg) and men 130-260 lbs (60-118kg), a 1-1½-inch needle is needed. For women weighing more than 200 lbs (90 kg) or men weighing more than 260 lbs (118 kg), a 1½-inch needle is required.

- **Technique**

  - Follow standard medication administration guidelines for site assessment/selection and site preparation.

  - To avoid injection into subcutaneous tissue, spread the skin of the selected vaccine administration site taut between the thumb and forefinger, isolating the muscle. Another technique, acceptable mostly for pediatric and geriatric patients, is to grasp the tissue and "bunch up" the muscle.

  - Insert the needle fully into the muscle at a 90° angle and inject the vaccine into the tissue.

  - Withdraw the needle and apply light pressure to the injection site for several seconds with a dry cotton ball or gauze.

• **Aspiration** - Aspiration is the process of pulling back on the plunger of the syringe prior to injection to ensure that the medication is not injected into a blood vessel. Although this practice is advocated by some experts, the procedure is not required because no large blood vessels exist at the recomended injection sites.



Intramuscular Administration Techniques

- **Multiple Vaccinations** - When administering multiple vaccines, NEVER mix vaccines in the same syringe unless approved for mixing by the Food and Drug Administration (FDA). If more than one vaccine must be administered in the same limb, the injection sites should be separated by 1-2 inches so that any local reactions can be differentiated. Vaccine doses range from 0.2 mL to 1 mL. The recommended maximum volume of medication for an IM site, varies among references and depends on the muscle mass of the individual. However, administering two IM vaccines into the same muscle would not exceed any suggested volume ranges for either the vastus lateralis or the deltoid muscle in any age group. The option to also administer a subcutaneous vaccine into the same limb, if necessary, is acceptable since a different tissue site is involved.

  If a vaccine and an immune globulin preparation are administered simultaneously (e.g., Td/Tdap and tetanus immune globulin [TIG] or hepatitis B vaccine and hepatitis B immune globulin [HBIG]), a separate anatomic site should be used for each injection. The location of each injection should be documented in the patient's medical record.

- **Nonstandard Administration** - Deviation from the recommended route, site and dosage of vaccine is strongly discouraged and can result in inadequate protection. In situations where nonstandard administration has occurred, refer to the ACIP General Recommendation on Immunization, *MMWR* 2006; 55 (RR-15), for specific guidance.

Special Situations

Bleeding Disorders - Individuals with a bleeding disorder or who are receiving anticoagulant therapy may develop hematomas in IM injection sites. Prior to administration of IM vaccines the patient or family should be instructed about the risk of hematoma formation from the injection. Additionally, a physician familiar with the patient's bleeding disorder or therapy should be consulted regarding the safety of administration by this route. If the patient periodically receives hemophilia replacement factor or other similar therapy, IM vaccine administration should ideally be scheduled shortly after replacement therapy. A 23-gauge or finer needle should be used and firm pressure applied to the site for at least 2 minutes. The site should not be rubbed or massaged.

Latex Allergy - Administration of a vaccine supplied in a vial or syringe that contains natural rubber (refer to product information) should not be administered to an individual with a history of a severe (anaphylactic) allergy to latex, unless the benefit of vaccination clearly outweighs the risk of an allergic reaction. These situations are rare. Medical consultation and direction should be sought regarding vaccination. A local or contact sensitivity to latex is not a contraindication to vaccination.

Syncopal or Vasovagal Response ("fainting") may occur during vaccine administration, especially with adolescents and adults. Because individuals may fall and sustain injury as a result, the provider should have the patient sit during injection(s). A syncopal or vasovagal response is not common and is not an allergic reaction. However, if syncope develops, the provider should observe and administer supportive care until the patient is recovered.

Anaphylaxis (a life-threatening acute allergic reaction) - Each facility that administers vaccines should have a protocol, procedures and equipment to provide initial care for suspected anaphylaxis. Facility staff should be prepared to recognize and respond appropriately to this type of emergency situation. All staff should maintain current CPR certification. Emergency protocols, procedures and equipment/supplies should be reviewed periodically. For additional information on medical management of vaccine reactions in children, teens, and adults, see the 2006 ACIP General Recommendations on Immunization (p. 19), the 2006 AAP *Red Book* (pp. 64-66), and pages D28-D31 of this appendix. Although both fainting and allergic reactions are rare, vaccine providers should strongly consider observing patients for 15 minutes after they are vaccinated.

Documentation

All vaccines administered should be fully documented in the patient's permanent medical record. Documentation should include:

1. Date of administration
2. Name or common abbreviation of vaccine
3. Vaccine lot number
4. Vaccine manufacturer

5. Administration site

6. Vaccine Information Statement (VIS) edition date (found in the lower right corner of the back of the VIS).

7. Name and address of vaccine administrator. This should be the address where the record is kept. If immunizations are given in a shopping mall, for example, the address would be the clinic where the permanent record will reside.

Facilities that administer vaccines are encouraged to participate in state/local immunization information systems. The patient or parent should be provided with an immunization record that includes the vaccines administered with dates of administration.

The California Department of Health Services' Immunization Branch has developed a complete package of resources on vaccine administration, available at http://www.eziz.org/pages/vaccineadmin.html

IMM-694B (9/01)

Skills Checklist for Immunization

The Skills Checklist is a self-assessment tool for health care staff who administer immunizations. To complete it, review the competency areas below and the clinical skills, techniques and procedures outlined for each of them. Score yourself in the Self-Assessment column. If you check **Need to Improve** you indicate further study, practice or change is needed. When you check **Meets or Exceeds** you indicate you believe you are performing at the expected level of competence, or higher.

Supervisors: Use the Skills Checklist to clarify responsibilities and expectations for staff who administer vaccines. When you use it for performance reviews, give staff the opportunity to score themselves in advance. Next observe their performance as they provide immunizations to several patients and score in the Supervisor Review columns. If improvement is needed, meet with them to develop a Plan of Action (over) that will help them achieve the level of competence you expect; circle desired actions or write in others. In 30 days, observe their performance again. When all competency areas meet expectations, file the Skills Checklist in their personnel folder. At the end of the probationary period and annually thereafter, observe them again and complete the Skills Checklist.

		Self-Assessment		Supervisor Review		
Competency	**Clinical Skills, Techniques, and Procedures**	**Need to Improve**	**Meets or Exceeds**	**Need to Improve**	**Meets or Exceeds**	**Plan of Action***
A. Patient/Parent Education	1. Welcomes patient/family, establishes rapport, and answers any questions.					
	2. Explains what vaccines will be given and which type(s) of injection will be done.					
	3. Accommodates language or literacy barriers and special needs of patient/parents to help make them feel comfortable and informed about the procedure.					
	4. Verifies patient/parents received the Vaccine Information Statements for indicated vaccines and had time to read them and ask questions.					
	5. Screens for contraindications. (MA: score NA–not applicable–if this is MD function.)					
	6. Reviews comfort measures and after care instructions with patient/parents, inviting questions.					
B. Medical Protocols	1. Identifies the location of the medical protocols (i.e. immunization protocol, emergency protocol, reference material).					
	2. Identifies the location of the epinephrine, its administration technique, and clinical situations where its use would be indicated.					
	3. Maintains up-to-date CPR certification.					
	4. Understands the need to report any needlestick injury and to maintain a sharps injury log.					
C. Vaccine Handling	1. Checks vial expiration date. Double-checks vial label and contents prior to drawing up.					
	2. Maintains aseptic technique throughout.					
	3. Selects the correct needle size. 1"-1 1/2" for IM (DTaP, Td, Hib, HepA, HepB, Pneumo Conj., Flu); 5/8" for SC (MMR, Var); IPV and Pneumo Poly depends on route to be used.					
	4. Shakes vaccine vial and/or reconstitutes and mixes using the diluent supplied. Inverts vial and draws up correct dose of vaccine. Rechecks vial label.					
	5. Labels each filled syringe or uses labeled tray to keep them identified.					
	6. Demonstrates knowledge of proper vaccine handling, e.g. protects MMR from light, logs refrigerator temperature.					

Competency	Clinical Skills, Techniques, and Procedures	Self-Assessment		Supervisor Review		
		Need to Improve	Meets or Exceeds	Need to Improve	Meets or Exceeds	Plan of Action*
D. Administering Immunizations	1. Rechecks the physician's order or instructions against prepared syringes.					
	2. Washes hands and if office policy puts on disposable gloves.					
	3. Demonstrates knowledge of the appropriate route for each vaccine. (IM for DTaP, Td, Hib, HepA, HepB, Pneumo Conj, Flu. SC for MMR, Var; Either SC or IM for IPV and Pneumo Poly).					
	4. Positions patient and/or restrains the child with parent's help; locates anatomic landmarks specific for IM or SC.					
	5. Preps the site with an alcohol wipe using a circular motion from the center to a 2" to 3" circle. Allows alcohol to dry.					
	6. Controls the limb with the non-dominant hand; holds the needle an inch from the skin and inserts it quickly at the appropriate angle (45º for SC or 90º for IM).					
	7. Injects vaccine using steady pressure; withdraws needle at angle of insertion.					
	8. Applies gentle pressure to injection site for several seconds with a dry cotton ball.					
	9. Properly disposes of needle and syringe in sharps container. Properly disposes of live vaccine vial.					
	10. Encourages comfort measures before, during and after the procedure.					
E. Records Procedures	1. Fully documents each immunization in patient's chart: date, lot number, manufacturer, site, VIS date, name/initials.					
	2. If applicable, demonstrates ability to use IZ registry or computer to call up patient record, assess what is due today, and update computer immunization history.					
	3. Asks for and updates patient's record of immunizations and reminds them to bring it to each visit.					

Plan of Action: **Circle desired next steps and write in the agreed deadline and date for the follow-up performance review.** **a.** Watch video on immunization techniques. **b.** Review office protocols. **c.** Review manuals, textbooks, wall charts or other guides. **d.** Review package inserts. **e.** Review vaccine handling guidelines or video. **f.** Observe other staff with patients. **g.** Practice injections. **h.** Read Vaccine Information Statements. **i.** Be mentored by someone who has these skills. **j.** Role play with other staff interactions with parents and patients, including age-appropriate comfort measures. **k.** Attend a skills training or other courses or training. **l.** Attend health care customer satisfaction or cultural competency training. **m.** Renew CPR certification. **Other:** _____

Employee Signature _____ Date _____

Supervisor Signature _____ Date _____

Plan of Action Deadline _____

Date of Next Performance Review _____

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For 8 1/2" x 11" copies, enlarge to 155%

Immunization Site Map

Suggested sites for infant immunizations:



RD: _____

LD: _____

RT: _____

RT: _____

LT: _____

LT: _____

RD= Right deltoid (IM) or subcutaneous tissue on upper arm (SC).

RT= Right vastus lateralis (IM) or subcutaneous tissue on thigh (SC).

LD= Left deltoid (IM) or subcutaneous tissue on upper arm (SC).

LT= Left vastus lateralis (IM) or subcutaneous tissue on thigh (SC).



IMMUNIZATION TECHNIQUES

California Department of Health Services • Immunization Branch • 2151 Berkeley Way • Berkeley, CA 94704

IMM-718 (5/01)

Immunization Site Map

Suggested sites for toddler immunizations:



RD: _____

LD: _____

RT: _____

RT: _____

LT: _____

LT: _____

RD= Right deltoid (IM) or subcutaneous tissue on upper arm (SC).

RT= Right vastus lateralis (IM) or subcutaneous tissue on thigh (SC).

LD= Left deltoid (IM) or subcutaneous tissue on upper arm (SC).

LT= Left vastus lateralis (IM) or subcutaneous tissue on thigh (SC).



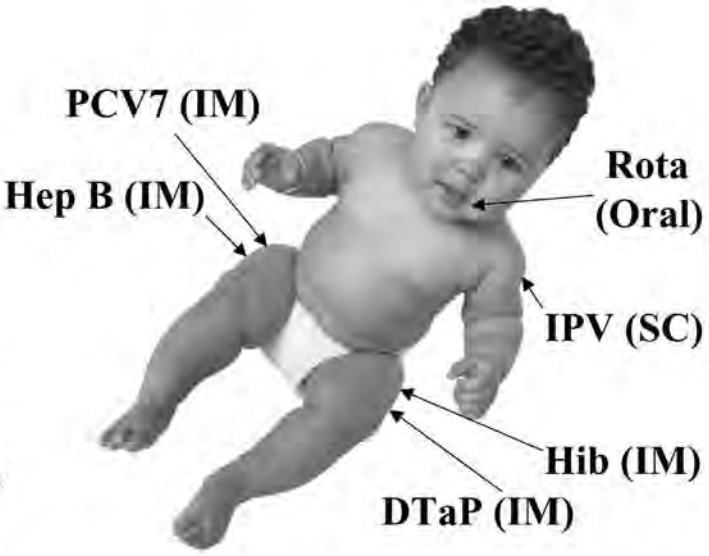
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IMM-718 (5/01)

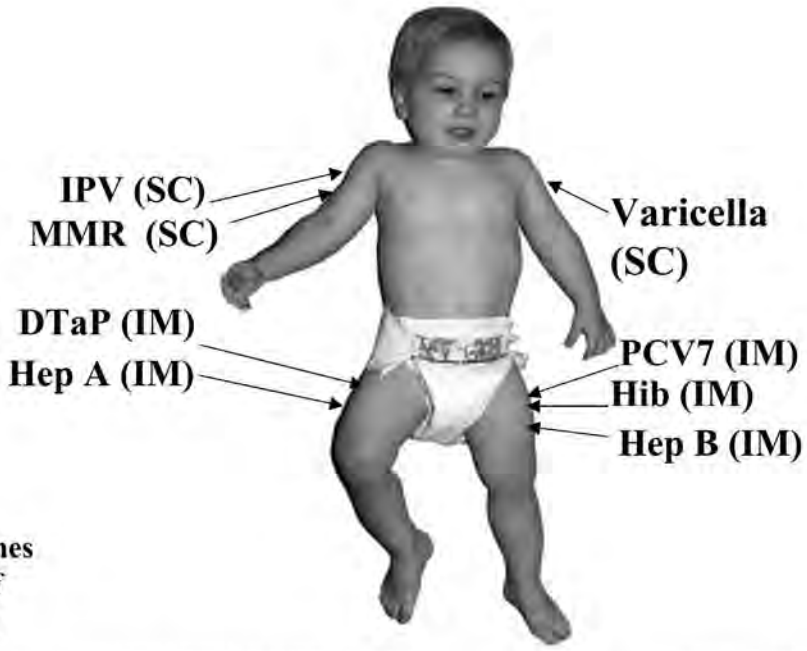
Giving All the Doses Under 12 Months

- Needle Lengths:
  IM=1 inch SC=5/8 inch
- Using combination vaccines will decrease the number of injections
- IM injections are given in the infant's thigh
- SC injections may be given in the arm or thigh
- Separate injection sites by 1-2 inches
- May consider a 5/8" needle for IM injections only in newborns less than 4 wks



Giving All the Doses 12 Months and Older

- Needle Lengths
  IM=1 to 1.5 inches
  SC=5/8 inch
- Separate injection sites by 1-2 inches
- Anterolateral thigh is the **preferred** site for multiple IM injections
- Deltoid (upper arm) is an option for IM in children ≥18 mo with adequate muscle mass
- Using **combination vaccines** will decrease the number of injections needed to keep a child up-to-date



Giving All the Doses 12 months through 5 years of age

Using Pediarix™ (DTaP/HepB/IPV) and ProQuad® (MMRV)

Pediarix™ can only be used for the primary series; DO NOT use for: 4th or 5th dose of DTaP, 4th dose of IPV



MMRV (SC) [ProQuad®]

DTaP/Hep B/IPV (IM) [Pediarix™]

HIB (IM)

PCV7 (IM)

Hep A (IM)

- Needle Lengths: IM = 1-1.5 inches SC = 5/8 inch
- Injection sites should be separated 1-2 inches
- The anterolateral thigh is the **preferred** site for multiple IM injections
- The deltoid (upper arm) is an option for IM in children ≥ 18 mo with adequate muscle mass

Using COMVAX™ (HepB/Hib) and ProQuad® (MMRV)



IPV (SC)

MMRV (SC) [ProQuad®]

DTaP (IM)

HepB/Hib (IM) [COMVAX™]

PCV7 (IM)

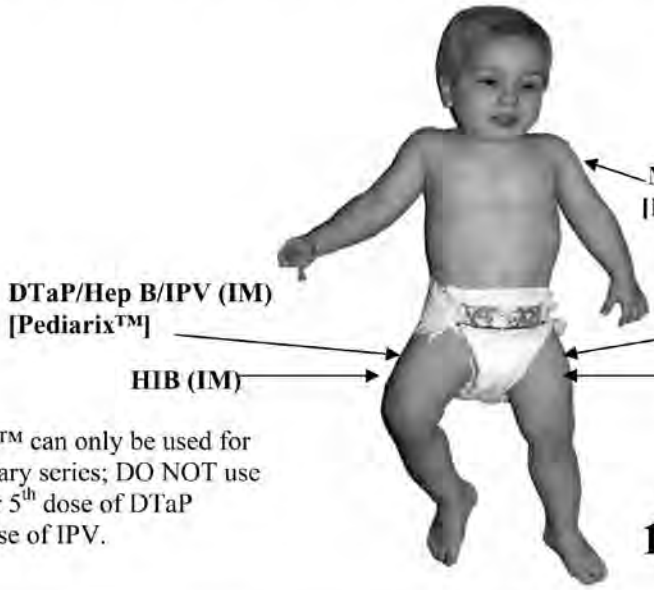
Hep A (IM)

Alliance for Immunization in Michigan
2007 AIM Kit – Childhood Section

August 23, 2006

Giving All the Doses Including Influenza Vaccine (TIV)

Using Pediarix™ (DTaP/HepB/IPV) and ProQuad® (MMR/Var)

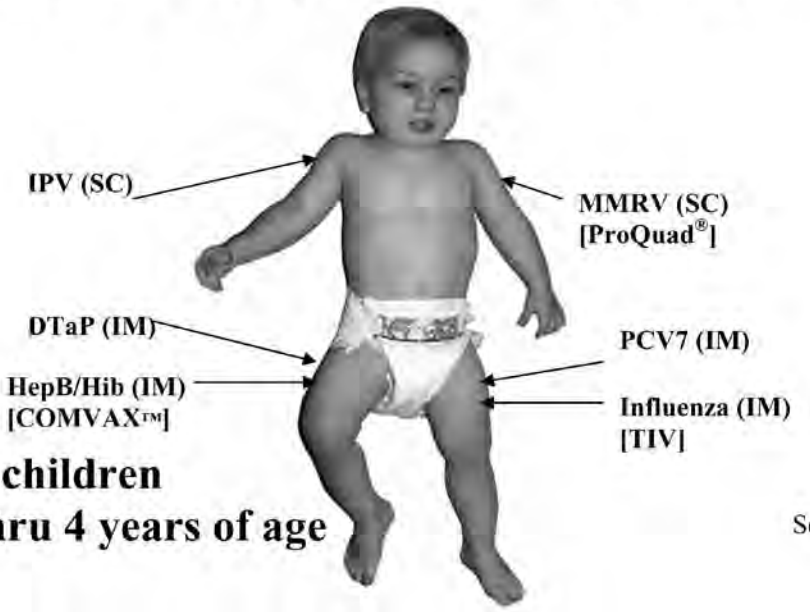


Pediarix™ can only be used for the primary series; DO NOT use for 4th or 5th dose of DTaP or 4th dose of IPV.

For children 12 thru 4 years of age

- TIV Dosages: 6-35 mos 0.25 mL; 3-8 yrs 0.5 mL
- 2 doses (4 weeks apart) are recommended for children 6 mo thru 8 yrs receiving any flu vaccine for the first time
- Children 6 mo-8 yrs who received influenza vaccine for the first time **during the previous influenza season**, and got only one dose, should receive two doses this season separated by 4 weeks

Using COMVAX™ (HepB/Hib) and ProQuad® (MMR/Var)



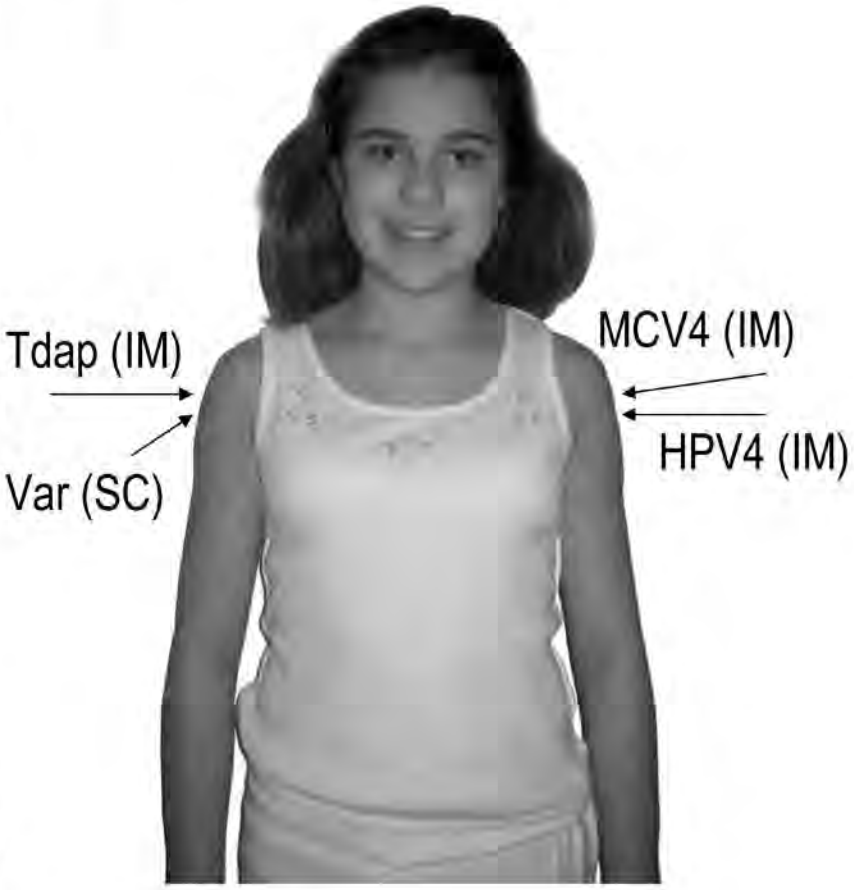
For children 12 months thru 4 years of age

September 21, 2007

GIVING ALL THE DOSES

11-12 Years of Age

- Needle Lengths
  IM= 1 to 1.5 in
  SC= 5/8 in
- Separate injection sites by 1-2 inches
- Professional judgment is appropriate when selecting needle length for use in all children, especially small infants or larger children.
- Assess for other recommended vaccines that may be needed-
  MMR Polio
  hep B Hep A
  influenza
- Syncope or fainting after vaccination may occur in adolescents & young adults, usually within 15 minutes of vaccination
- When giving vaccines to teens:
  Have the patient sit down while you are giving vaccine(s)
  Consider observing patients for 15-20 minutes after vaccination



NOTE:
Var should be administered to school age children and adolescents without:

- history of 2 doses of varicella vaccine
- a healthcare provider's diagnosis of varicella disease **or** verification of history of typical varicella disease
- history of shingles

HPV4 is licensed for use in **girls only** 9-26 years of age
MMRV (ProQuad®) is licensed for children 12 months thru 12 years of age only

Alliance for Immunization in Michigan
2008 AIM Kit—Adolescent Immunization Section
December 6, 2007

COMFORTING RESTRAINT

FOR IMMUNIZATIONS

• The method:

This method involves the parent in embracing the child and controlling all four limbs. It avoids "holding down" or overpowering the child, but it helps you steady and control the limb of the injection site.

• For infants and toddlers:







Have parent hold the child on parent's lap.

1. One of the child's arms embraces the parent's back and is held under the parent's arm.
2. The other arm is controlled by the parent's arm and hand. For infants, the parent can control both arms with one hand.
3. Both legs are anchored with the child's feet held firmly between the parent's thighs, and controlled by the parent's other arm.

• For kindergarten and older children:





Hold the child on parent's lap or have the child stand in front of the seated parent.

1. Parent's arms embrace the child during the process.
2. Both legs are firmly between parent's legs.

IMMUNIZATION TECHNIQUES
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Gray Davis, Governor—State of California
Grantland Johnson, Secretary—Health and Human Services Agency
Diana M. Bontá, R.N., Dr.P.H., Director—Department of Health Services
Immunization Branch • 2151 Berkeley Way • Berkeley, CA 94704

IMM-720 (12/01)

Injectable Vaccine Administration for Children Birth-6 years

Vaccine	Age/Reminders	Route	Site ¤	Needle*	Contraindications ⊕
Diphtheria, Tetanus, Pertussis (DTaP)	6 weeks-6 years	IM	Anterolateral Thigh **or** Deltoid±	1"-1.5" 22-25 g	Anaphylactic reaction to prior dose or component; encephalopathy without other cause within 7 days of a pertussis- containing vaccine
Haemophilus influenza type B (Hib)	No routine doses after 59 months	IM	Anterolateral Thigh **or** Deltoid	1"-1.5" 22-25 g	Anaphylactic reaction to prior dose or component
Pneumococcal conjugate (PCV7)	No routine doses after 59 months	IM	Anterolateral Thigh **or** Deltoid	1"-1.5" 22-25 g	Anaphylactic reaction to prior dose or component
Hepatitis B (Hep B)	1st dose at birth; last dose at/after 6 months	IM	Anterolateral Thigh **or** Deltoid	1"-1.5" 22-25 g	Anaphylactic reaction to a prior dose or component (baker's yeast)
Inactivated Polio Vaccine (IPV)	For school entry: 1st dose at/ after 6 wks of age; all doses spaced at least 4 weeks apart	SC	Anterolateral Thigh **or** Lateral Upper Arm	5/8" 23-25 g	Anaphylactic reaction to a prior dose or component (neomycin, streptomycin, polymyxin B)
		IM	Anterolateral Thigh **or** Deltoid	1"-1.5 22-25 g	
Measles, Mumps, Rubella (MMR)	1st dose at/after 12 mo; 4 week interval between two doses (all ages)	SC	Anterolateral Thigh **or** Lateral Upper Arm	5/8" 23-25 g	Anaphylactic reaction to a prior dose or component (neomycin or gelatin); pregnancy
Varicella (Var)	1st dose at/after 12 mo; 3 mo interval between doses (ages 12 mo-12 yrs)	SC	Anterolateral Thigh **or** Lateral Upper Arm	5/8" 23-25 g	Anaphylactic reaction to a prior dose or component (neomycin or gelatin); pregnancy
Inactivated Influenza (TIV)	6 months and older; brand to use based on age	IM	Anterolateral Thigh **or** Deltoid	1"-1.5" 22-25 g	Anaphylactic reaction to a prior dose or component (eggs)
Hepatitis A (Hep A)	1st dose at/after 12 mo 2nd dose 6 mo later	IM	Anterolateral Thigh **or** Deltoid	1"-1.5" 22-25 g	Anaphylactic reaction to prior dose or component; hypersensitivity to alum (Havrix®: 2-phenoxyethanol)

¤ Vaccines should never be administered in the buttocks. ⊕ See package insert for complete contraindication/component listing; may vary by brand * Professional judgment is appropriate when selecting needle length for use in all children, especially small infants or larger children.

± Use of the deltoid muscle in children 18 months and older (if adequate muscle mass is present) is an option for IM injections. December 11, 2007

Injectable Vaccines for Selected Populations**

Vaccine	Recommendations for use and age	Route	Site ¤	Needle Length*	Contraindications⊕
Meningococcal Conjugate » (MCV4)	• For children 2-10 yrs who are at high risk for meningococcal disease •Routinely given to adolescents (1 dose) ages 11 through 18 yrs	IM	Anterolateral Thigh **or** Deltoid ±	1"-1.5" 22-25 g	Anaphylactic reaction to prior dose or component
Pneumococcal polysaccharide (PPV 23)	• For children 2 yrs and older at high risk for invasive pneumococcal disease • Given after completion of an age-appropriate PCV7 series - Minimum interval of 8 weeks between PCV7 and PPV23	IM	Anterolateral Thigh **or** Deltoid ±	1"-1.5" 22-25 g	Anaphylactic reaction to prior dose or component
		SC	Anterolateral Thigh **or** Lateral Upper Arm	5/8" 23-25g	

¤ Vaccines should never be administered in the buttocks.
* Professional judgment is appropriate when selecting needle length for use in all children, especially small infants or larger children.
⊕ See package insert for complete contraindication/component listing; components may vary by brand used
» When meningococcal vaccine is indicated and MCV4 is not available, Meningococcal polysaccharide (MPSV4) may be used for persons 2 years and older (given SC). However, if indication is for routine adolescent vaccination (ages 11-18 years), defer until MCV4 is available.
± Use of the deltoid muscle in children 18 months and older (if adequate muscle mass is present) is an option for IM injections.
** Refer to Recommended Childhood and Adolescent Immunization Schedule (available in Child/Adolescent Immunization Section of the AIM Kit) for information on the selected populations.

Injectable Vaccine Administration for Children 7-18 Years

Vaccine	Age/Reminders	Route	Site*	Needle*	Contraindications ⊕
Tetanus, diphtheria (Td)	7 years and older	IM	Deltoid	1"-1.5" 22-25 g	Anaphylactic reaction to prior dose or component
Tetanus, diphtheria, pertussis (Tdap)	Routinely given at age 11-12 years; one dose ◙	IM	Deltoid	1"-1.5" 22-25 g	Anaphylactic reaction to prior dose or component; encephalopathy within 7 days of previous pertussis vaccine without other known cause
Hepatitis B (hep B)	1st dose at birth; last dose at/after 6 mo	IM	Deltoid	1"-1.5" 22-25 g	Anaphylactic reaction to a prior dose or component (baker's yeast)
Inactivated Polio Vaccine (IPV)	For school entry: 1st dose at/after 6 wks of age; all doses spaced at least 4 weeks apart	SC	Lateral Upper Arm	5/8" 23-25 g	Anaphylactic reaction to a prior dose or component (neomycin, streptomycin, or polymyxin B)
		IM	Deltoid	1"-1.5" 22-25 g	
Measles, Mumps, Rubella (MMR)	1st dose at/after12 mo	SC	Lateral Upper Arm	5/8" 23-25 g	Anaphylactic reaction to a prior dose or component (neomycin, gelatin); pregnancy
Varicella (Var)	1st dose at/after 12 mo 12mo-12 yr: 3 months between dose 1 & 2	SC	Lateral Upper Arm	5/8" 23-25 g	Anaphylactic reaction to a prior dose or component (neomycin, gelatin); pregnancy
Inactivated Influenza (TIV)	Assure vaccine brand being used is age-appropriate	IM	Deltoid	1"-1.5" 22-25 g	Anaphylactic reaction to a prior dose or component (eggs)
Meningococcal Conjugate (MCV4)	Routinely given at age 11-12 yrs; catch-up all adolescents 13-18 yrs	IM	Deltoid	1"-1.5" 22-25 g	Anaphylactic reaction to a prior dose or component; history of GBS
Human Papilloma-virus (HPV4)	Females 9 through 26 years	IM	Deltoid	1"-1.5" 22-25 g	Anaphylactic reaction to prior dose or component; hypersensitivity to baker's yeast
Hepatitis A (hep A)	1st dose at/after 12 mo 2nd dose 6 mo later	IM	Deltoid	1"-1.5" 22-25 g	Anaphylactic reaction to prior dose or component; hypersensitivity to alum (Havrix®: 2-phenoxyethanol)

* Professional judgment is appropriate when selecting needle length and administration site; do not administer vaccines in buttocks

⊕ See package insert for complete contraindication listing; components may vary by brand of vaccine used

◙ Two Tdap vaccines available: Boostrix® (GSK) is licensed for persons 10-18 yrs; ADACEL™ (sanofi pasteur) licensed for persons 11-64 yrs.

December 14, 2007

Injectable Vaccines for Selected Populations**

Vaccine	Recommendation for use and age	Route	Site*	Needle Length*	Contraindications⊕
Meningococcal Polysaccharide (MPSV4)	• For children 2 years and older at high risk for meningococcal disease **and** MCV4 (conjugate) is not available • For persons with a history of Guillain-Barre syndrome (GBS)	SC	Lateral Upper Arm	5/8" 23-25g	Anaphylactic reaction to prior dose of component
Pneumococcal polysaccharide (PPV 23)	• For children 2 yrs and older at high risk for invasive pneumococcal disease • Given after completion of an age-appropriate PCV7 series - Minimum interval of 8 weeks between PCV7 and PPV23	IM	Deltoid	1"-1.5" 22-25 g	Anaphylactic reaction to prior dose or component
		SC	Lateral Upper Arm	5/8" 23-25g	

*Professional judgment is appropriate when selecting needle length and administration site; do not administer vaccines in buttocks

⊕ See package insert for complete contraindication listing; components may vary by brand of vaccine used

** Refer to Recommended Childhood and Adolescent Immunization Schedule (available in Child/Adolescent Immunization Section of the AIM Kit on online at www.cdc.gov/vaccines) for information on the selected populations.

Medical Management of Vaccine Reactions in Children and Teens

All vaccines have the potential to cause an adverse reaction. To minimize adverse reactions, patients should be carefully screened for precautions and contraindications before vaccine is administered. Even with careful screening, reactions can occur. These reactions can vary from trivial and inconvenient (e.g., soreness, itching) to severe and life threatening (e.g., anaphylaxis). If reactions occur, staff should be prepared with procedures for their management. The table below describes procedures to follow if various reactions occur.

Reaction	Symptoms	Management
Localized	Soreness, redness, itching, or swelling at the injection site	Apply a cold compress to the injection site. Consider giving an analgesic (pain reliever) or antipruritic (anti-itch) medication.
	Slight bleeding	Apply an adhesive compress over the injection site.
	Continuous bleeding	Place thick layer of gauze pads over site and maintain direct and firm pressure; raise the bleeding injection site (e.g., arm) above the level of the patient's heart.
Psychological fright and syncope (fainting)	Fright before injection is given	Have patient sit or lie down for the vaccination.
	Extreme paleness, sweating, coldness of the hands and feet, nausea, light-headedness, dizziness, weakness, or visual disturbances	Have patient lie flat or sit with head between knees for several minutes. Loosen any tight clothing and maintain an open airway. Apply cool, damp cloths to patient's face and neck.
	Fall, without loss of consciousness	Examine the patient to determine if injury is present before attempting to move the patient. Place patient flat on back with feet elevated.
	Loss of consciousness	Check the patient to determine if injury is present before attempting to move the patient. Place patient flat on back with feet elevated. Call 911 if patient does not recover immediately.
Anaphylaxis	Sudden or gradual onset of generalized itching, erythema (redness), or urticaria (hives); angioedema (swelling of the lips, face, or throat); severe bronchospasm (wheezing); shortness of breath; shock; abdominal cramping; or cardiovascular collapse	See "Emergency Medical Protocol for Management of Anaphylactic Reactions in Children and Teens" on the next page for detailed steps to follow in treating anaphylaxis.

Supplies Needed

- ☐ Aqueous epinephrine 1:1000 dilution, in ampules, vials of solution, or prefilled syringes, including epinephrine auto-injectors (e.g., EpiPen). If EpiPens are to be stocked, both EpiPen Jr. (0.15 mg) and adult EpiPens (0.30 mg) should be available.
- ☐ Diphenhydramine (Benadryl) injectable (50 mg/mL solution) and oral (12.5 mg/5 mL suspension) and 25 mg or 50 mg capsules or tablets
- ☐ Syringes: 1–3 cc, 22–25g, 1", 1½", and 2" needles for epinephrine and diphenhydramine (Benadryl)
- ☐ Pediatric & adult airways (small, medium, and large)
- ☐ Sphygmomanometer (child, adult & extra-large cuffs) and stethoscope
- ☐ Pediatric & adult size pocket masks with one-way valve
- ☐ Alcohol swabs
- ☐ Tongue depressors
- ☐ Flashlight with extra batteries (for examination of mouth and throat)
- ☐ Wrist watch
- ☐ Tourniquet
- ☐ Cell phone or access to an on-site phone

(Page 1 of 2)

www.immunize.org/catg.d/p3082a.pdf • Item #P3082a (8/06)

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Emergency Medical Protocol for Management of Anaphylactic Reactions in Children and Teens

Signs and Symptoms of Anaphylactic Reaction

Sudden or gradual onset of generalized itching, erythema (redness), or urticaria (hives); angioedema (swelling of the lips, face, or throat); bronchospasm (wheezing); shortness of breath; shock; abdominal cramping; or cardiovascular collapse.

Treatment in Children and Teens

a. If itching and swelling are confined to the injection site where the vaccination was given, observe patient closely for the development of generalized symptoms.

b. If symptoms are generalized, activate the emergency medical system (EMS; e.g., call 911) and notify the on-call physician. This should be done by a second person, while the primary nurse assesses the airway, breathing, circulation, and level of consciousness of the patient.

c. Administer aqueous epinephrine 1:1000 dilution (i.e., 1 mg/mL) intramuscularly; the standard dose is 0.01 mg/kg body weight, up to 0.3 mg maximum single dose in children and 0.5 mg maximum in adolescents (see chart below).

d. In addition, for anaphylaxis, administer diphenhydramine either orally or by intramuscular injection; the standard dose is 1 mg/kg body weight, up to 30 mg maximum dose in children and 100 mg maximum dose in adolescents (see chart below).

e. Monitor the patient closely until EMS arrives. Perform cardiopulmonary resuscitation (CPR), if necessary, and maintain airway. Keep patient in supine position (flat on back) unless he or she is having breathing difficulty. If breathing is difficult, patient's head may be elevated, provided blood pressure is adequate to prevent loss of consciousness. If blood pressure is low, elevate legs. Monitor blood pressure and pulse every 5 minutes.

f. If EMS has not arrived and symptoms are still present, repeat dose of epinephrine every 10–20 minutes for up to 3 doses, depending on patient's response.

g. Record all vital signs, medications administered to the patient, including the time, dosage, response, and the name of the medical personnel who administered the medication, and other relevant clinical information.

h. Notify the patient's primary care physician.

Suggested Dosing of Epinephrine and Diphenhydramine

Age Group Dose	Weight * in kg	Weight (lbs)* in lbs	Epinephrine Dose 1 mg/mL injectable (1:1000 dilution) intramuscular	Diphenhydramine (Benadryl) 12.5 mg/5 mL liquid 25 and 50 mg capsules or tabs 50 mg/mL injectable
1–6 mos	4–7 kg	9–15 lbs	0.05 mg (0.05 ml)	5 mg
7–18 mos	7–11 kg	15–24 lbs	0.1 mg (0.1 ml)	10 mg
19–36 mos	11–14 kg	24–31 lbs	0.15 mg (0.15 ml)	15 mg
37–48 mos	14–17 kg	31–37 lbs	0.15 mg (0.15 ml)	20 mg
49–59 mos	17–19 kg	37–42 lbs	0.2 mg (0.2 ml)	
5–7 yrs	19–23 kg	42–51 lbs	0.2 mg (0.2 ml)	30 mg
8–10 yrs	23–35 kg	51–77 lbs	0.3 mg (0.3 ml)	
11–12 yrs	35–45 kg	77–99 lbs	0.4 mg (0.4 ml)	40 mg
13 yrs & older	45+ kg	99+ lbs	0.5 mg (0.5 ml)	50–100 mg

*Dosing by body weight is preferred.

These standing orders for the medical management of vaccine reactions in child and teenage patients shall remain in effect for patients of the _____ (*name of clinic*) until rescinded or until _____ (*date*).

Medical Director's signature _____ Effective date _____

Sources: American Academy of Pediatrics. Passive Immunization. In: Pickering LK, ed. *Red Book: 2006 Report of the Committee on Infectious Diseases*. 27th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2006: 64–66.

American Pharmacists Association, Grabenstein, JD. *Pharmacy-Based Immunization Delivery*, 2002.

Medical Management of Vaccine Reactions in Adult Patients

All vaccines have the potential to cause an adverse reaction. In order to minimize adverse reactions, patients should be carefully screened for precautions and contraindications before vaccine is administered. Even with careful screening, reactions may occur. These reactions can vary from trivial and inconvenient (e.g., soreness, itching) to severe and life threatening (e.g., anaphylaxis). If reactions occur, staff should be prepared with procedures for their management. The table below describes procedures to follow if various reactions occur.

Reaction	Symptoms	Management
Localized	Soreness, redness, itching, or swelling at the injection site	Apply a cold compress to the injection site. Consider giving an analgesic (pain reliever) or antipruritic (anti-itch) medication.
	Slight bleeding	Apply an adhesive compress over the injection site.
	Continuous bleeding	Place thick layer of gauze pads over site and maintain direct and firm pressure; raise the bleeding injection site (e.g., arm) above the level of the patient's heart.
Psychological fright and syncope (fainting)	Fright before injection is given	Have patient sit or lie down for the vaccination.
	Extreme paleness, sweating, coldness of the hands and feet, nausea, light-headedness, dizziness, weakness, or visual disturbances	Have patient lie flat or sit with head between knees for several minutes. Loosen any tight clothing and maintain an open airway. Apply cool, damp cloths to patient's face and neck.
	Fall, without loss of consciousness	Examine the patient to determine if injury is present before attempting to move the patient. Place patient flat on back with feet elevated.
	Loss of consciousness	Check the patient to determine if injury is present before attempting to move the patient. Place patient flat on back with feet elevated. Call 911 if patient does not recover immediately.
Anaphylaxis	Sudden or gradual onset of generalized itching, erythema (redness), or urticaria (hives); angioedema (swelling of the lips, face, or throat); severe bronchospasm (wheezing); shortness of breath; shock; abdominal cramping; or cardiovascular collapse.	See "Emergency Medical Protocol for Management of Anaphylactic Reactions in Adults" on the next page for detailed steps to follow in treating anaphylaxis.

(continued on page 2)

"Clinical content modified by the Centers for Disease Control and Prevention, Nov. 2005"

www.immunize.org/catg.d/p3082.pdf • Item #P3082 (11/06)

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(continued from page 1)

Emergency Medical Protocol for Management of Anaphylactic Reactions in Adults

Supplies Needed

- ☐ Aqueous epinephrine 1:1000 (i.e., 1 mg/mL) dilution, in ampules, vials of solution, or prefilled syringes, including epinephrine autoinjectors (e.g., EpiPen). If EpiPens are stocked, at least three adult EpiPens (0.30 mg) should be available.
- ☐ Diphenhydramine (Benadryl) injectable (50 mg/mL solution) and 25 mg or 50 mg capsules or tablets and syrup (12.5 mg/5 mL suspension)
- ☐ Syringes: 1–3 cc, 22–25g, 1", 1½", and 2" needles for epinephrine and diphenhydramine (Benadryl)
- ☐ Wristwatch with second hand
- ☐ Adult airways (small, medium, and large)
- ☐ Sphygmomanometer (adult and extra-large cuffs) and stethoscope
- ☐ Adult size pocket mask with one-way valve
- ☐ Alcohol swabs
- ☐ Tourniquet
- ☐ Tongue depressors
- ☐ Flashlight with extra batteries (for examination of the mouth and throat)
- ☐ Cell phone or access to an on-site phone

Signs and Symptoms of Anaphylactic Reaction

Sudden or gradual onset of generalized itching, erythema (redness), or urticaria (hives); angioedema (swelling of the lips, face, or throat); bronchospasm (wheezing); shortness of breath; shock; abdominal cramping; or cardiovascular collapse.

Treatment in Adults

a. If itching and swelling are confined to the injection site where the vaccination was given, observe patient closely for the development of generalized symptoms.

b. If symptoms are generalized, activate the emergency medical system (EMS; e.g., call 911) and notify the on-call physician. This should be done by a second person, while the primary nurse assesses the airway, breathing, circulation, and level of consciousness of the patient.

c. Administer aqueous epinephrine 1:1000 dilution intramuscularly, 0.01 mL/kg/dose (adult dose ranges from 0.3 mL to 0.5 mL, with maximum single dose of 0.5 mL).

d. In addition, for systemic anaphylaxis, administer diphenhydramine either orally or by intramuscular injection; the standard dose is 1–2 mg/kg, up to 100 mg maximum single dose.

e. Monitor the patient closely until EMS arrives. Perform cardiopulmonary resuscitation (CPR), if necessary, and maintain airway. Keep patient in supine position (flat on back) unless he or she is having breathing difficulty. If breathing is difficult, patient's head may be elevated, provided blood pressure is adequate to prevent loss of consciousness. If blood pressure is low, elevate legs. Monitor blood pressure and pulse every 5 minutes.

f. If EMS has not arrived and symptoms are still present, repeat dose of epinephrine every 10–20 minutes for up to 3 doses, depending on patient's response.

g. Record all vital signs, medications administered to the patient, including the time, dosage, response, and the name of the medical personnel who administered the medication, and other relevant clinical information.

h. Notify the patient's primary care physician.

Sources: 1. American Academy of Pediatrics. Passive Immunization. In: Pickering LK, ed. *Red Book: 2006 Report of the Committee on Infectious Diseases*. 27th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2006:64–66.
2. American Pharmacists Association, Grabenstein, JD. *Pharmacy-Based Immunization Delivery*, 2002.
3. *Got Your Shots? A Providers Guide to Immunizations in Minnesota*. Second Edition, Minnesota Department of Health, 2001:80-82.

These standing orders for the medical management of vaccine reactions in adult patients shall remain in effect for patients of the _____ (*name of clinic*) until rescinded or until _____ (*date*).

_____ Medical Director's signature

_____ Effective date

APPENDIX E
Vaccine Information Statements

It's Federal Law **E-1**

Instructions for Use of VISs **E-2**

How to Get Vaccine Information Statements **E-3**

VIS Questions and Answers **E-4**

CDC's Vaccine Information Statement Webpage **E-8**

Appendix E

It's federal law!

You must give your patients current Vaccine Information Statements (VISs)

As healthcare professionals understand, the risks of serious consequences following vaccination are many hundreds or thousands of times less likely than the risks associated with the diseases that the vaccines protect against. Most adverse reactions from vaccines are mild and self-limited. Serious complications are rare, but they can have a devastating effect on the recipient, family members, and the providers involved with the care of the patient. We must continue the efforts to make vaccines as safe as possible.

Equally important is the need to furnish vaccine recipients (or the parents/legal representatives of minors) with objective information on vaccine safety and the diseases that the vaccines protect against, so that they are actively involved in making decisions affecting their health or the health of their children. When people are not informed about vaccine adverse events, even common, mild events, they can lose their trust in healthcare providers and vaccines. Vaccine Information Statements (VISs) provide a standardized way to present objective information about vaccine benefits and adverse events.

What are VISs?

VISs are developed by the staff of the Centers for Disease Control and Prevention (CDC) and undergo intense scrutiny by panels of experts for accuracy. Each VIS provides information to properly inform the adult vaccine recipient or the minor child's parent or legal representative about the risks and benefits of each vaccine. VISs are not meant to replace interactions with healthcare providers, who should answer questions and address concerns that the recipient or the parent/legal representative may have.

Use of the VIS is mandatory!

Before a healthcare provider vaccinates a child or an adult with a dose of any vaccine containing diphtheria, tetanus, pertussis, measles, mumps, rubella, polio, hepatitis A, hepatitis B, *Haemophilus influenzae* type b (Hib), influenza, pneumococcal conjugate, meningococcal, rotavirus, human papillomavirus (HPV), or varicella (chickenpox) vaccine, the provider is required by the National Childhood Vaccine Injury Act (NCVIA) to provide a copy of the VIS to either the adult recipient or to the child's parent/legal representative.

VISs are also available for pneumococcal polysaccharide vaccine, as well as various vaccines used primarily for international travelers. The use of these VISs is recommended but not currently required by federal law.

An alternative VIS—the multi-vaccine VIS—is an option to providing single-vaccine VISs when administering one or more of these routine birth-through-6-month vaccines: DTaP, hepatitis B, Hib, pneumococcal (PCV), polio (IPV), or rotavirus (RV). The multi-vaccine VIS can also be used when giving combination birth-through-6-month vaccines (i.e., Pediarix or Comvax) or when giving two or more routine birth-through-6-month vaccines together at other pediatric visits (e.g., 12–15 months or 4–6 years).

State or local health departments or individual providers may place the clinic name on the VISs, but any other changes must be approved by the director of CDC's National Center for Immunization and Respiratory Diseases.

What to do with VISs

Some of the legal requirements concerning the use of VISs are as follows:

1. Before an NCVIA-covered vaccine is administered to anyone (this includes adults!), you must give the patient or the parent/legal representative a copy of the most current VIS available for that vaccine. Make sure you give your patient time to read the VIS prior to the administration of the vaccine.
2. You must record in your patient's chart the date the VIS was given.
3. You must also record on the patient's chart the publication date of the VIS, which appears on the bottom of the VIS.

How to get VISs

All available VISs can be downloaded from the website of the Immunization Action Coalition at www.immunize.org/vis or from CDC's website at www.cdc.gov/vaccines/pubs/vis/default.htm. Ready-to-copy versions may also be available from your state or local health department.

Non-English language versions of VISs are not available from CDC; however, several state health departments have arranged for their translations. These versions do not require CDC approval. You can find VISs in more than 30 languages on the Immunization Action Coalition website at www.immunize.org/vis. To find VISs in alternative formats (e.g., audio, web-video), go to: www.immunize.org/vis/vis_audio.asp.

To obtain a complete set of current VISs in more than 30 languages, visit IAC's website at www.immunize.org/vis

Most current versions of VISs

As of December 2008, the most recent versions of the VISs are as follows:

DTaP/DT/DTP	5/17/07	PCV	12/9/08
hepatitis A	3/21/06	PPSV	7/29/97
hepatitis B	7/18/07	polio	1/1/00
Hib	12/16/98	rabies	1/12/06
HPV (human papillomavirus)	2/2/07	rotavirus	8/28/08
influenza (LAIV)	7/24/08	shingles	9/11/06
influenza (TIV)	7/24/08	Td/Tdap	11/18/08
Japan. enceph.	5/11/05	typhoid	5/19/04
meningococcal	1/28/08	varicella	3/13/08
MMR	3/13/08	yellow fever	11/9/04

Multi-vaccine VIS 9/18/08
(for 6 vaccines given to infants/children: DTaP, IPV, Hib, Hep B, PCV, RV)

"We have an obligation to provide patients and/or parents with information that includes both the benefits and the risks of vaccines. This can be done with the Vaccine Information Statements that healthcare providers are required by law to provide prior to the administration of vaccines."

Walter A. Orenstein, MD, past director, National Immunization Program, CDC

Technical content reviewed by the Centers for Disease Control and Prevention: December 2008

Instructions for the Use of
Vaccine Information Statements

Required Use

1. Provide Vaccine Information Statement (VIS) when vaccination is given.

As required under the National Childhood Vaccine Injury Act (42 U.S.C. §300aa-26), all health care providers in the United States who administer, to any child or adult, diphtheria, tetanus, pertussis, measles, mumps, rubella, polio, hepatitis A, hepatitis B, *Haemophilus influenzae* type b (Hib), trivalent influenza, pneumococcal conjugate, meningococcal, rotavirus, human papillomavirus (HPV), or varicella (chickenpox) vaccines shall, prior to administration of each dose of the vaccine, provide a copy to keep of the relevant current edition vaccine information materials that have been produced by the Centers for Disease Control and Prevention (CDC):

- to the parent or legal representative* of any child to whom the provider intends to administer such vaccine, and
- to any adult to whom the provider intends to administer such vaccine. (In the case of an incompetent adult, relevant VISs shall be provided to the individual's legal representative.* If the incompetent adult is living in a long-term care facility, all relevant VISs may be provided at the time of admission, or at the time of consent if later than admission, rather than prior to each immunization.)

If there is not a single VIS for a combination vaccine, use the VISs for all component vaccines.

The materials shall be supplemented with visual presentations or oral explanations, as appropriate.

*"Legal representative" is defined as a parent or other individual who is qualified under State law to consent to the immunization of a minor child or incompetent adult.

2. Record information for each VIS provided.

Health care providers shall make a notation in each patient's permanent medical record at the time vaccine information materials are provided, indicating:
(1) the edition date of the Vaccine Information Statement distributed, and
(2) the date the VIS was provided.

This recordkeeping requirement supplements the requirement of 42 U.S.C. §300aa-25 that all health care providers administering these vaccines must record in the patient's permanent medical record (or in a permanent office log):
(3) the name, address and title of the individual who administers the vaccine,
(4) the date of administration, and
(5) the vaccine manufacturer and lot number of the vaccine used.

Applicability of State Law

Health care providers should consult their legal counsel to determine additional State requirements pertaining to immunization. The Federal requirement to provide the vaccine information materials supplements any applicable State laws.

Availability of Copies

Single camera-ready copies of the vaccine information materials are available from State health departments. Copies are also available on CDC's website at www.cdc.gov/vaccines/pubs/vis.

Copies are available in English and in other languages.

Reference 42 U.S.C. §300aa-26

12/9/08

Current VIS Editions

Diphtheria, Tetanus, Pertussis (DTaP/DT): 5/17/07
Haemophilus influenzae type b: 12/16/98
Hepatitis A: 3/21/06
Hepatitis B: 7/18/07
Human Papillomavirus (HPV): 2/2/07
Inactivated Influenza: 7/24/08
Live, Intranasal Influenza: 7/24/08
Measles, Mumps, Rubella (MMR): 3/13/08
Meningococcal: 1/28/08
Pneumococcal conjugate: 12/9/08
Polio: 1/1/00
Rotavirus: 8/28/08
Tetanus, Diphtheria, (Pertussis) (Td/Tdap): 11/18/08
Varicella (chickenpox): 3/13/08
Multi-Vaccine*: 9/18/08

* This VIS is as an optional alternative when two or more routine childhood vaccines (i.e., DTaP, hepatitis B, Hib, pneumococcal, polio, or rotavirus) are administered at the same visit.

Where to Get Vaccine Information Statements

1. **The Internet.** All current VISs are available on the internet from two websites:
   - CDC (www.cdc.gov/vaccines/pubs/vis/default.htm)
   - The Immunization Action Coalition (www.immunize.org/vis/)

   VISs from these sites can be downloaded as pdf files and printed.

2. **CDC's Immunization Works CD.** This CD contains pdf files for all VIS (current as of the date the CD was issued). *Immunization Works* is usually available at CDC's immunization booth at conferences or can be ordered through CDC's online publications order form at https://www2a.cdc.gov/nchstp_od/PIWeb/niporderform.asp.

3. **State Health Departments.** CDC sends each state health department's immunization program camera-ready copies when a new VIS is published. The programs, in turn, can provide copies to providers within the state.

Audio files for most VISs can be downloaded from CDC's VIS webpage.

Text versions of VISs can also be accessed from CDC's VIS webpage. These files are compatible with screen-reader devices for use by the vision-impared.

Translations of many VISs are available in more than 30 languages from the Immunization Action Coalition's website (www.immunize.org/vis/index.htm). Languages available include:

Arabic	French	Korean	Samoan
Armenian	German	Laotian	Serbo-Croatian
Bosnian	Haitian	Marshallese	Somali
Burmese	Hindi	Polish	Spanish
Cambodian	Hmong	Porguguese	Tagalog
Chinese	Ilokano	Punjabi	Thai
Croatian	Italian	Romanian	Turkish
Farsi	Japanese	Russian	Vietnamese

Appendix E

Questions & Answers: Vaccine Information Statements

1. **Should the VISs be used for adults getting vaccines as well as for children?**

   Yes. Under the National Childhood Vaccine Injury Act, anyone receiving a covered vaccine should be given the appropriate VIS. VISs for vaccines that are administered to both adults and children are worded so they may be used by both.

2. **Are VISs "informed consent" forms?**

   No. People sometimes use the term "informed consent" loosely when referring to VISs. But even when vaccine information materials had tear-off sheets for parents to sign, they were not technically informed consent forms. The signature was simply to confirm that the "Duty to Warn" clause in the vaccine contract was being fulfilled.

   There is no Federal requirement for informed consent. VISs are written to fulfill the information requirements of the National Childhood Vaccine Injury Act. But because they cover both benefits and risks associated with vaccinations, they provide enough information that anyone reading them should be adequately informed. Some states have informed consent laws, covering either procedural requirements (e.g., whether consent may be oral or must be written) or substantive requirements (e.g., types of information required). Check your state medical consent law to determine if there are any specific informed consent requirements relating to immunization. VISs can be used for informed consent as long as they conform to the appropriate state laws.

3. **The law states that vaccine information materials be given to a child's legal representatives. Is this the same as "legal guardian?"**

   Not necessarily. A "legal representative" is a parent or other individual who is qualified under state law to consent to the immunization of a minor. It does not have to be the child's legal guardian (e.g., it could be a grandparent). There is not an overriding Federal definition.

4. **Must the patient, parent, or legal representative physically take away a copy of each VIS, or can we simply let them read a copy and make sure they understand it?**

   Ideally the person getting the shot, or their representative, should actually take each VIS home. VISs contain information that may be useful later (e.g., the recommended vaccine schedule, information about what to do in the case of an adverse reaction). Patients may choose not to take the VIS, but the provider must offer them the opportunity to do so.

5. **When do providers have to start using a new VIS?**

   The date for a new VISs required use is announced when the final draft is published in the Federal Register. Ideally, providers will begin using a new VIS immediately, particularly if the vaccine's contraindications or adverse event profile have changed significantly since the previous version.

6. **How should we comply with the law for patients who cannot read the VISs (e.g., those who are illiterate or blind)?**

   The National Childhood Vaccine Injury Act requires providers to supplement the VISs with "visual

presentations" or "oral explanations" as needed. If patients are unable to read the VISs, it is up to the provider to ensure that they have access to the information they contain. VISs can be read to these patients, or videotapes can be used as supplements. At least one CD-ROM is being produced on which users can hear the VIS's read. Audio files and versions of VISs that are compatible with screen reader devices are available on CDC's VIS website.

7. Why are the dates on some of the VISs so old? Are they obsolete? Why can't they be updated every year?

VISs are updated only when they need to be. For instance, a VIS would be updated if there were a change in ACIP recommendations that affected the vaccine's adverse event profile, indications, or contraindications. If VISs were dated annually, there would be multiple editions in circulation that were identical but would have different dates. As it is, only the most recently-dated VIS for each vaccine is valid. VISs posted on CDC's VIS webpage will always be current, regardless of the edition date.

8. Sometimes a VIS contains recommendations that is at odds with the manufacturer's package insert. Why?

VISs are based on the ACIP's recommendations, which occasionally differ from those made by the manufacturer. These differences may involve adverse events. For example, a package insert may mention all adverse events that were temporally associated with a vaccine during clinical trials, whereas ACIP tends to recognize only those likely to be causally linked to the vaccine.

9. What is the reading level of VISs?

Defining the readibility of a VIS by a traditional "grade level" measure can be difficult and misleading. Two criteria used in standard readability formulas are word length and sentence length. Neither is necessarily a reliable measure of readability. There are multi-syllable words that are widely understood and short words that are not. VISs often use bulleted lists, which a readability program might see as very long sentences (no period), even though they are actually quite easy to understand.

Applying a Fletch-Kincaid test to a VIS usually shows about a 10th grade reading level, but this should be taken with the caveats mentioned above.

In what may be a more useful measure of readability, several VISs were the subject of a series of focus groups among low literacy parents in a variety of racial and ethnic groups (including non-native English speakers) in 1998, and the participants overwhelmingly rated them easy to read and understand. Another round of focus groups is scheduled to be conducted soon, probably in 2009.

10. Which VISs must be used?

The appropriate VIS must be provided to the recipient of any vaccine covered by the National Childhood Vaccine Injury Act (NVCIA). VISs are available for all vaccines licensed in the United States (except BCG). Their use is strongly encouraged, whether mandated by the NCVIA or not.

11. May providers develop their own vaccine information materials or modify the VISs?

Providers who administer vaccines covered by the National Childhood Vaccine Injury Act are required to use the official CDC VISs. However, providers may supplement the VISs with materials of their own. Health departments or providers may add clinic name and contact information to a VIS as long as no other changes are made. Any other addition to these documents or variations from their language or format must have the prior written approval of the Director of CDC's National Center for Immunization and Respiratory Diseases.

12. How should we distribute VISs when the parent or legal representative of a minor is not present at the time the vaccination is given, for example during a school-based adolescent vaccination program?

CDCs legal advisors have proposed two alternatives for this situation:

- *Consent Prior to Administration of Each Dose of a Series*. With this alternative the VIS must be mailed or sent home with the student around the time of administration of each dose. Only those children for whom a signed consent is returned may be vaccinated. The program must place the signed consent in the patient's medical record.

- *Single Signature for Series.* This alternative is permissible only in those States where a single consent to an entire vaccination series is allowed under State law and in those schools where such a policy would be acceptable. The first dose of vaccine may be administered only after the parent or legal representative receives a copy of the VIS and signs and returns a statement that a) acknowledges receipt of the VIS and provides permission for their child to be vaccinated with the complete series of the vaccine (if possible, list the approximate dates of future doses); and b) acknowledges their acceptance of the following process regarding administration of additional doses:

  Prior to administration of each dose following the initial dose, a copy of the VIS will be mailed to the parent (or legal representative) who signs the original consent at the address they provide on this statement, or the VIS will be sent home with the student; and

  The vaccine information statements for the additional doses will be accompanied by a statement notifying the parent that, based on their earlier permission, the next dose will be administered to their child (state the date), unless the parent returns a portion of this statement by mail to an address provided, to arrive prior to the intended vaccination date, in which the parent withdraws permission for the child to receive the remaining doses.

The program must maintain the original consent signature and any additional dose veto statements in the patient's medical record. A record must be kept of the dates prior to additional doses that the VIS was mailed, or sent home with the adolescent.

Prior to administration of each additional dose, the provider should ask the adolescent whether he/she experienced any significant adverse events following receipt of earlier doses. If yes, the provider should consider consulting the parent or delaying the vaccination. The adolescent's response to questions about adverse reactions to previous doses should be kept in the medical record.

The following questions concern CDC's Multi-Vaccine VIS (www.cdc.gov/vaccines/pubs/vis/downloads/vis-multi.pdf).

13. Why was a Multi-Vaccine VIS developed?

It was developed with the earliest pediatric visits (i.e., birth through 6 months) in mind. Up to 6 vaccinations could be given during these visits, meaning (for the provider) that 6 individual VISs would have to be downloaded, printed and distributed and (for the patient) 6 documents would have to be read, containing much information that is duplicated. The multi-vaccine VIS is an effort to simplify and streamline this process.

14. May the existing, single-vaccine VISs still be used?

Yes. The Multi-Vaccine VIS an optional alternative to existing VISs. Providers wishing to continue using the

individual VISs may do so. These will continue to be updated when recommendations change, as they have always been.

15. Must all 6 vaccines be given at the same visit for the Multi-Vaccine VIS to be used?

No. Any time two or more of the vaccines are given together it makes sense to use the Multi-Vaccine VIS. The provider should check the appropriate boxes on the first page, corresponding to vaccines given during that visit.

16. May the Multi-Vaccine VIS be used with combination vaccines, such as Pediarix or Comvax?

Yes. Just check the appropriate boxes on the first page as you would if you were administrating the individual vaccines.

17. When we record the edition date of the VISs in the patient's medical record, do we record the date on the Multi-Vaccine VIS or the dates for the individual VISs?

If you use the Multi-Vaccine VIS, record its date for each of the vaccines given that day. If there is ever a question, this will make it clear that the Multi-Vaccine VIS was used and not the individual VISs.

18. Can the Multi-Vaccine VIS be used for children older than 6 months, or for adolescents or adults getting any of these same vaccines?

It may be used for older children getting two or more of these vaccines during the same visit (e.g., a 12-month old getting Hib and PCV, or a 4-year old getting DTaP and IPV). However it should not be used for adolescents or adults. The information on this document applies to pediatric use of the vaccines. Risk factors that apply only to older persons, for example, are not discussed on this VIS. The individual VISs should be used.

19. May the Multi-Vaccine VIS be used for catch-up doses?

Yes, as long as the doses are given to children as part of the primary series or routine pediatric boosters.

20. The Multi-Vaccine VIS covers "pneumococcal" vaccine. Is it just for PCV7, or may it also be used when PPV23 is given to children?

It was designed with PCV7 specifically in mind. For PPV23, use the single VIS.

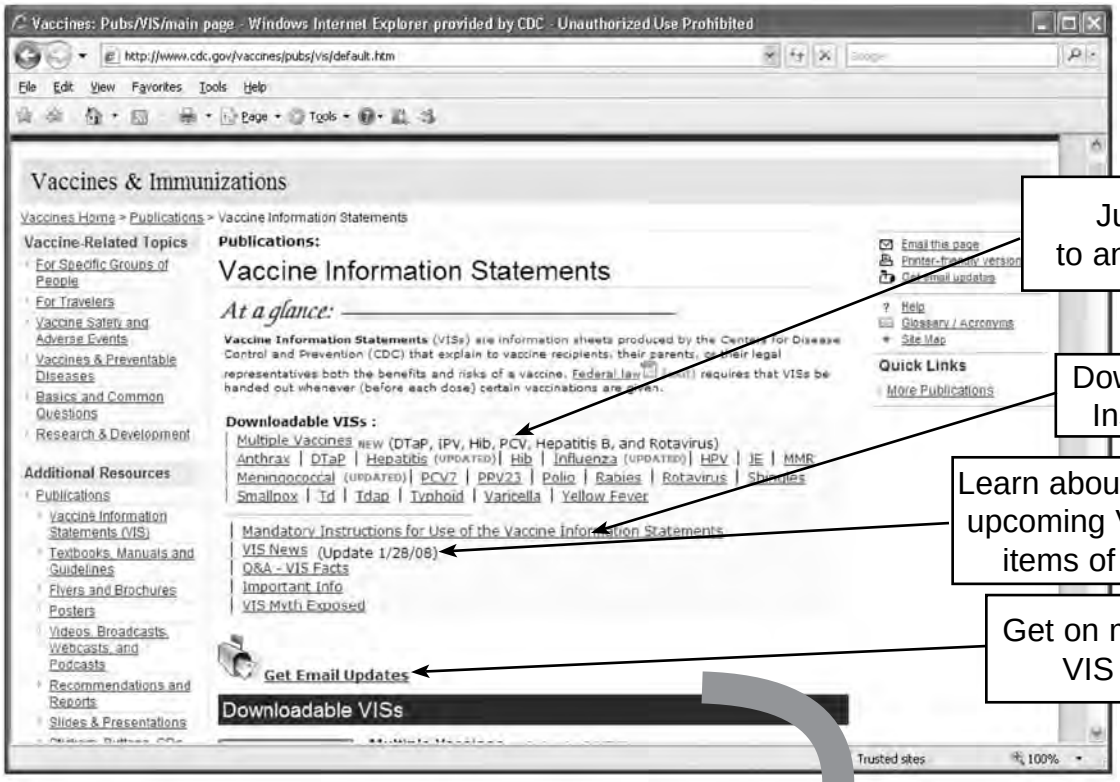
21. Will there be other Multi-Vaccine VISs, for example, for vaccines administered at 12-months or during the pre-school or adolescent-visits?

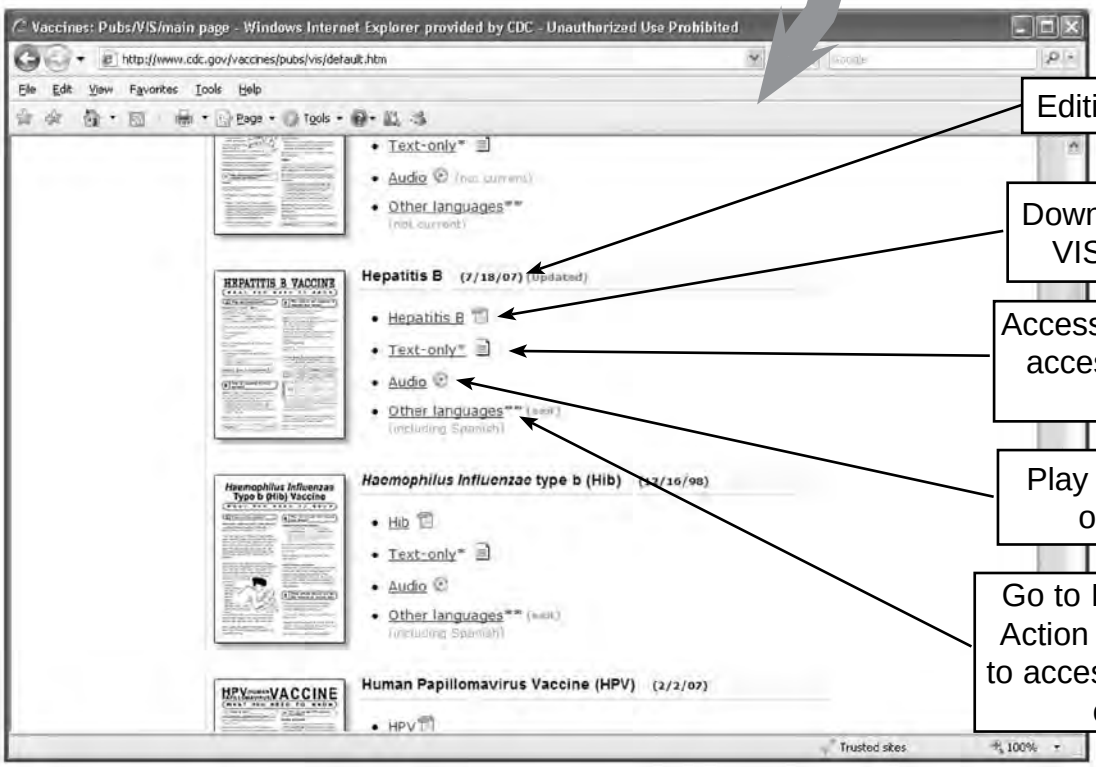
There is a multi-vaccine VIS for adolescents in development now, and plans to develop one for the 12-month vaccines as well.

Appendix E

CDC's Vaccine Information Statement Webpage

http://www.cdc.gov/vaccines/pubs/vis/default.htm





E

APPENDIX F
Vaccine Safety

The Vaccine Adverse Event Reporting System (VAERS) F-1

Table of Reportable Events Following Vaccination F-2

Vaccine Adverse Event Reporting System (VAERS) Form F-4

The Vaccine Injury Compensation Program (VICP) F-6

The VICP Vaccine Injury Table F-7

"Qualifications and Aids to Interpretation of Vaccine Injury Table" F-8

Appendix F

The Vaccine Adverse Event Reporting System (VAERS)

VAERS is a national vaccine safety surveillance program co-sponsored by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA). VAERS collects and analyzes information from reports of adverse events following immunization. Since 1990, VAERS has received over 123,000 reports, most of which describe mild side effects such as fever. Very rarely, people experience serious adverse events following immunization. By monitoring such events, VAERS can help to identify important new safety concerns.

Reporting to VAERS

Who can file a VAERS report: Anyone can submit a VAERS report. Most reports are sent in by vaccine manufacturers (42%) and health care providers (30%). The rest are submitted by state immunization programs (12%), vaccine recipients or their parent/guardians (7%), and other sources (9%).

What adverse events should be reported: VAERS encourages the reporting of any clinically significant adverse event that occurs after the administration of any vaccine licensed in the United States. Report such events even if you are unsure whether a vaccine caused them.

The National Childhood Vaccine Injury Act (NCVIA) requires health care providers to report:

- Any event listed by the vaccine manufacturer as a contraindication to subsequent doses of the vaccine.
- Any event listed in the Reportable Events Table that occurs within the specified time period after vaccination.

A copy of the Reportable Events Table can be found on the next page (F-2), or obtained by calling VAERS at 1-800-822-7967 or by downloading it from http://vaers.hhs.gov/pubs.htm.

Filing a VAERS report: Use a VAERS report form (see page F-4) to report any adverse event. You can get pre-addressed postage paid report forms by calling VAERS at 1-800-822-7967, or download a printable copy of the VAERS form from the following Internet sites:

- The VAERS Web site at http://vaers.hhs.gov/
- The Food and Drug Administration's Web site at www.fda.gov/cber/vaers/vaers.htm
- The Centers for Disease Control and Prevention Web site at www.cdc.gov/vaccines/

Instructions are included with the form. You may use a photocopy of the VAERS form to submit a report.

For more information:

- Send e-mail inquiries to info@vaers.org
- Visit the VAERS Web site at: http://vaers.hhs.gov
- Call the toll-free VAERS information line at (800) 822-7967
- Fax inquiries to the toll-free information fax line at (877) 721-0366

This information has been adapted from the VAERS website (http://vaers.hhs.gov).

Appendix F

VAERS Table of Reportable Events Following Vaccination*

Vaccine/Toxoid	Event	Interval from Vaccination
Tetanus in any combination; DTaP, DTP, DTP-HiB, DT, Td, TT, Tdap	A. Anaphylaxis or anaphylactic shock B. Brachial neuritis C. Any acute complications or sequela (including death) of above events D. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	7 days 28 days Not applicable See package insert
Pertussis in any combination; DTaP, DTP, DTP-HiB, P, Tdap	A. Anaphylaxis or anaphylactic shock B. Encephalopathy (or encephalitis) C. Any acute complications or sequela (including death) of above events D. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	7 days 7 days Not applicable See package insert
Measles, mumps and rubella in any combination; MMR, MR, M, MMRV, R	A. Anaphylaxis or anaphylactic shock B. Encephalopathy (or encephalitis) C. Any acute complications or sequela (including death) of above events D. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	7 days 15 days Not applicable See package insert
Rubella in any combination; MMR, MMRV, MR, R	A. Chronic arthritis B. Any acute complications or sequela (including death) of above event C. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	42 days Not applicable See package insert
Measles in any combination; MMR, MMRV, MR, M	A. Thrombocytopenic purpura B. Vaccine-strain measles viral infection in an immunodeficient recipient C. Any acute complications or sequela (including death) of above events D. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	7-30 days 6 months Not applicable See package insert
Oral Polio (OPV)	A. Paralytic polio – in a non-immunodeficient recipient – in an immunodeficient recipient – in a vaccine associated community case B. Vaccine-strain polio viral infection – in a non-immunodeficient recipient – in an immunodeficient recipient – in a vaccine associated community case C. Any sequela (including death) of above events D. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	 30 days 6 months Not applicable 30 days 6 months Not applicable Not applicable See package insert
Inactivated Polio (IPV)	A. Anaphylaxis or anaphylactic shock B. Any sequela (including death) of the above event C. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	7 days Not applicable See package insert
Hepatitis B	A. Anaphylaxis or anaphylactic shock B. Any acute complications or sequela (including death) of the above event C. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	7 days Not applicable See package insert
Hemophilus influenzae type b (conjugate)	A. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert
Varicella	A. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert
Rotavirus	A. Intussusception B. Any acute complications or sequela (including death) of the above event C. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	30 days Not applicable See package insert
Pneumococcal conjugate	A. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert
Hepatitis A	A. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert
Influenza	A. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert

* **Effective date: July 01, 2005.** The Reportable Events Table (RET) reflects what is reportable by law (42 USC 300aa-25) to the Vaccine Adverse Event Reporting System (VAERS) including conditions found in the manufacturers package insert. In addition, individuals are encouraged to report **any** clinically significant or unexpected events (even if you are not certain the vaccine caused the event) for **any** vaccine, whether or not it is listed on the RET. Manufacturers are also required by regulation (21CFR 600.80) to report to the VAERS program all adverse events made known to them for any vaccine.

Reportable Events Table Definitions

Anaphylaxis and anaphylactic shock. Anaphylaxis and anaphylactic shock mean an acute, severe, and potentially lethal systemic allergic reaction. Most cases resolve without sequelae. Signs and symptoms begin minutes to a few hours after exposure. Death, if it occurs, usually results from airway obstruction caused by laryngeal edema or bronchospasm and may be associated with cardiovascular collapse.

Brachial neuritis is defined as dysfunction limited to the upper extremity nerve plexus (i.e., its trunks, division, or cords) without involvement of other peripheral (e.g., nerve roots or a single peripheral nerve) or central (e.g., spinal cord) nervous system structures. A deep, steady, often severe aching pain in the shoulder and upper arm usually heralds onset of the condition. The pain is followed in days or weeks by weakness and atrophy in upper extremity muscle groups. Sensory loss may accompany the motor deficits, but is generally a less notable clinical feature.

Encephalopathy. For purposes of the Reportable Events Table, a vaccine recipient shall be considered to have suffered an encephalopathy only if such recipient manifests, within the applicable period, an injury meeting the description below of an acute encephalopathy, and then a chronic encephalopathy persists in such person for more than 6 months beyond the date of vaccination.

1. An ***acute encephalopathy*** is one that is sufficiently severe so as to require hospitalization (whether or not hospitalization occurred).
   a. For ***children less than 18 months of age*** who present without an associated seizure event, an acute encephalopathy is indicated by a "significantly decreased level of consciousness" (see "D" below) lasting for at least 24 hours. Those children less than 18 months of age who present following a seizure shall be viewed as having an acute encephalopathy if their significantly decreased level of consciousness persists beyond 24 hours and cannot be attributed to a postictal state (seizure) or medication.
   b. For adults and ***children 18 months of age*** or older, an acute encephalopathy is one that persists for at least 24 hours and is characterized by at least two of the following:
      i. A significant change in mental status that is not medication related: specifically a confusional state, or a delirium, or a psychosis;
      ii. A significantly decreased level of consciousness, which is independent of a seizure and cannot be attributed to the effects of medication; and
      iii. A seizure associated with loss of consciousness.
   c. Increased intracranial ***pressure*** may be a clinical feature of acute encephalopathy in any age group.
2. A "***significantly decreased level of consciousness***" is indicated by the presence of at least one of the following clinical signs for at least 24 hours or greater:
   a. Decreased or absent response to environment (responds, if at all, only to loud voice or painful stimuli);
   b. Decreased or absent eye contact (does not fix gaze upon family members or other individuals); or
   c. Inconsistent or absent responses to external stimuli (does not recognize familiar people or things).

   The following clinical features alone, or in combination, do not demonstrate an acute encephalopathy or a significant change in either mental status or level of consciousness as described above: Sleepiness, irritability (fussiness), high-pitched and unusual screaming, persistent inconsolable crying, and bulging fontanelle. Seizures in themselves are not sufficient to constitute a diagnosis of encephalopathy. In the absence of other evidence of an acute encephalopathy, seizures shall not be viewed as the first symptom or manifestation of the onset of an acute encephalopathy.
3. ***Chronic Encephalopathy*** occurs when a change in mental or neurologic status, first manifested during the applicable time period, persists for a period of at least 6 months from the date of vaccination. Individuals who return to a normal neurologic state after the acute encephalopathy shall not be presumed to have suffered residual neurologic damage from that event; any subsequent chronic encephalopathy shall not be presumed to be a sequela of the acute encephalopathy. If a preponderance of the evidence indicates that a child's chronic encephalopathy is secondary to genetic, prenatal or perinatal factors, that chronic encephalopathy shall not be considered to be a condition set forth in the Table.
   An encephalopathy shall not be considered to be a condition set forth in the Table if it is shown that the encephalopathy was caused by an infection, a toxin, a metabolic disturbance, a structural lesion, a genetic disorder or trauma (without regard to whether the cause of the infection, toxin, trauma, metabolic disturbance, structural lesion or genetic disorder is known).

Chronic Arthritis. For purposes of the Reportable Events Table, chronic arthritis may be found in a person with no history in the 3 years prior to vaccination of arthropathy (joint disease) on the basis of:

a. Medical documentation, recorded within 30 days after the onset, of objective signs of acute arthritis (joint swelling) that occurred between 7 and 42 days after a rubella vaccination; and
b. Medical documentation (recorded within 3 years after the onset of acute arthritis) of the persistence of objective signs of intermittent or continuous arthritis for more than 6 months following vaccination.
c. Medical documentation of an antibody response to the rubella virus.

The following shall not be considered as chronic arthritis: Musculoskeletal disorders such as diffuse connective tissue diseases (including but not limited to rheumatoid arthritis, juvenile rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, mixed connective tissue disease, polymyositis/dermatomyositis, fibromyalgia, necrotizing vasculitis and vasculopathies and Sjogren's Syndrome), degenerative joint disease, infectious agents other than rubella (whether by direct invasion or as an immune reaction), metabolic and endocrine diseases, trauma, neoplasms, neuropathic disorders, bone and cartilage disorders and arthritis associated with ankylosing spondylitis, psoriasis, inflammatory bowel disease, Reiter's syndrome, or blood disorders.

Arthralgia (joint pain) or stiffness without joint swelling shall not be viewed as chronic arthritis.

Sequela. The term "sequela" means a condition or event, which was actually caused by a condition listed in the Reportable Events Table.

Appendix F

WEBSITE: www.vaers.hhs.gov E-MAIL: info@vaers.org FAX: 1-877-721-0366

VACCINE ADVERSE EVENT REPORTING SYSTEM
24 Hour Toll-Free Information 1-800-822-7967
P.O. Box 1100, Rockville, MD 20849-1100
PATIENT IDENTITY KEPT CONFIDENTIAL

VAERS

For CDC/FDA Use Only
VAERS Number _____
Date Received _____

Patient Name:
Last First M.I.
Address
City State Zip
Telephone no. (___) _____

Vaccine administered by (Name):
Responsible Physician _____
Facility Name/Address
City State Zip
Telephone no. (___) _____

Form completed by (Name):
Relation to Patient ☐ Vaccine Provider ☐ Patient/Parent ☐ Manufacturer ☐ Other
Address *(if different from patient or provider)*
City State Zip
Telephone no. (___) _____

1. State	2. County where administered	3. Date of birth mm / dd / yy	4. Patient age	5. Sex ☐ M ☐ F	6. Date form completed mm / dd / yy

7. Describe adverse events(s) (symptoms, signs, time course) and treatment, if any

8. Check all appropriate:
☐ Patient died (date mm / dd / yy)
☐ Life threatening illness
☐ Required emergency room/doctor visit
☐ Required hospitalization (_____ days)
☐ Resulted in prolongation of hospitalization
☐ Resulted in permanent disability
☐ None of the above

9. Patient recovered ☐ YES ☐ NO ☐ UNKNOWN

10. Date of vaccination mm / dd / yy
Time _____ AM PM

11. Adverse event onset mm / dd / yy
Time _____ AM PM

12. Relevant diagnostic tests/laboratory data

13. Enter all vaccines given on date listed in no. 10

	Vaccine (type)	Manufacturer	Lot number	Route/Site	No. Previous Doses
a.					
b.					
c.					
d.					

14. Any other vaccinations within 4 weeks prior to the date listed in no. 10

	Vaccine (type)	Manufacturer	Lot number	Route/Site	No. Previous doses	Date given
a.						
b.						

15. Vaccinated at:
☐ Private doctor's office/hospital ☐ Military clinic/hospital
☐ Public health clinic/hospital ☐ Other/unknown

16. Vaccine purchased with:
☐ Private funds ☐ Military funds
☐ Public funds ☐ Other/unknown

17. Other medications

18. Illness at time of vaccination (specify)

19. Pre-existing physician-diagnosed allergies, birth defects, medical conditions (specify)

20. Have you reported this adverse event previously?
☐ No ☐ To health department ☐ To doctor ☐ To manufacturer

Only for children 5 and under
22. Birth weight _____ lb. _____ oz.
23. No. of brothers and sisters

21. Adverse event following prior vaccination (check all applicable, specify)

	Adverse Event	Onset Age	Type Vaccine	Dose no. in series
☐ In patient				
☐ In brother or sister				

Only for reports submitted by manufacturer/immunization project
24. Mfr./imm. proj. report no.
25. Date received by mfr./imm.proj.
26. 15 day report? ☐ Yes ☐ No
27. Report type ☐ Initial ☐ Follow-Up

Health care providers and manufacturers are required by law (42 USC 300aa-25) to report reactions to vaccines listed in the Table of Reportable Events Following Immunization. Reports for reactions to other vaccines are voluntary except when required as a condition of immunization grant awards.

Form VAERS-1 (FDA)

"Fold in thirds, tape & mail — DO NOT STAPLE FORM"

NO POSTAGE
NECESSARY
IF MAILED
IN THE
UNITED STATES
OR APO/FPO

BUSINESS REPLY MAIL
FIRST-CLASS MAIL PERMIT NO. 1895 ROCKVILLE, MD

POSTAGE WILL BE PAID BY ADDRESSEE

VAERS
P.O. Box 1100
Rockville MD 20849-1100

DIRECTIONS FOR COMPLETING FORM

(Additional pages may be attached if more space is needed.)

GENERAL

- Use a separate form for each patient. Complete the form to the best of your abilities. Items 3, 4, 7, 8, 10, 11, and 13 are considered essential and should be completed whenever possible. Parents/Guardians may need to consult the facility where the vaccine was administered for some of the information (such as manufacturer, lot number or laboratory data.)
- Refer to the Reportable Events Table (RET) for events mandated for reporting by law. Reporting for other serious events felt to be related but not on the RET is encouraged.
- Health care providers other than the vaccine administrator (VA) treating a patient for a suspected adverse event should notify the VA and provide the information about the adverse event to allow the VA to complete the form to meet the VA's legal responsibility.
- These data will be used to increase understanding of adverse events following vaccination and will become part of CDC Privacy Act System 09-20-0136, "Epidemiologic Studies and Surveillance of Disease Problems". Information identifying the person who received the vaccine or that person's legal representative will not be made available to the public, but may be available to the vaccinee or legal representative.
- Postage will be paid by addressee. Forms may be photocopied (must be front & back on same sheet).

SPECIFIC INSTRUCTIONS

Form Completed By: To be used by parents/guardians, vaccine manufacturers/distributors, vaccine administrators, and/or the person completing the form on behalf of the patient or the health professional who administered the vaccine.

Item 7: Describe the suspected adverse event. Such things as temperature, local and general signs and symptoms, time course, duration of symptoms, diagnosis, treatment and recovery should be noted.

Item 9: Check "YES" if the patient's health condition is the same as it was prior to the vaccine, "NO" if the patient has not returned to the pre-vaccination state of health, or "UNKNOWN" if the patient's condition is not known.

Item 10 and 11: Give dates and times as specifically as you can remember. If you do not know the exact time, please indicate "AM" or "PM" when possible if this information is known. If more than one adverse event, give the onset date and time for the most serious event.

Item 12: Include "negative" or "normal" results of any relevant tests performed as well as abnormal findings.

Item 13: List ONLY those vaccines given on the day listed in Item 10.

Item 14: List any other vaccines that the patient received within 4 weeks prior to the date listed in Item 10.

Item 16: This section refers to how the person who gave the vaccine purchased it, not to the patient's insurance.

Item 17: List any prescription or non-prescription medications the patient was taking when the vaccine(s) was given.

Item 18: List any short term illnesses the patient had on the date the vaccine(s) was given (i.e., cold, flu, ear infection).

Item 19: List any pre-existing physician-diagnosed allergies, birth defects, medical conditions (including developmental and/or neurologic disorders) for the patient.

Item 21: List any suspected adverse events the patient, or the patient's brothers or sisters, may have had to previous vaccinations. If more than one brother or sister, or if the patient has reacted to more than one prior vaccine, use additional pages to explain completely. For the onset age of a patient, provide the age in months if less than two years old.

Item 26: This space is for manufacturers' use only.

Appendix F

Vaccine Injury Compensation Program (VICP)

The VICP is a no-fault alternative to the traditional tort system for resolving vaccine injury claims. It was established as part of the National Childhood Vaccine Injury Act of 1986, after a rash of lawsuits against vaccine manufacturers and healthcare providers threatened to cause vaccine shortages and reduce vaccination rates.

The VICP covers all vaccines recommended by the Centers for Disease Control and Prevention for routine administration to children. It is administered jointly by the U.S. Department of Health and Human Services (HHS), the U.S. Court of Federal Claims (the Court), and the U.S. Department of Justice (DOJ). The VICP is located in the HRSA Healthcare Systems Bureau. Covered vaccines and compensible injuries are described on the "Vaccine Injury Table" (see following page - F7).

The Claims Process

An individual claiming a vaccine-related injury or death files a petition for compensation with the Court, and may be represented by an attorney. The Secretary of HHS is named as the Respondent.

An HHS physician reviews the petition to determine whether it meets the medical criteria for compensation. This recommendation is provided to the Court through a Respondent's report filed by the DOJ. The HHS position is presented by an attorney from the DOJ in hearings before a "special master," who makes the decision for compensation under the VICP. A decision may be appealed to the Court, then to the Federal Circuit Court of Appeals, and eventually to the U.S. Supreme Court.

If a case is found eligible for compensation, the amount of the award is usually negotiated between the DOJ and the petitioner's attorneys. If the attorneys can't agree, the case is scheduled for a hearing for the special master to assess the amount of compensation. Compensable claims, and even most claims found to be non-compensable, are awarded reimbursement for attorney's fees and costs. A petitioner may file a claim in civil court against the vaccine company and/or the vaccine administrator only after first filing a claim under the VICP and then rejecting the decision of the Court.

For more information, including information about restrictions that apply to filing a petition, visit the VICP website at http://www.hrsa.gov/vaccinecompensation or phone 1-800-338-2382.

For information on the Rules of the Court, including requirements for filing a petition, visit the Court's Website at http://www.uscfc.uscourts.gov/osmPage.htm or phone (202) 357-6400.

This information has been adapted from the VICP website (http://www.hrsa.gov/vaccinecompensation)

National Childhood Vaccine Injury Act: Vaccine Injury Table[a]

Vaccine	Adverse Event	Time Interval
I Tetanus toxoid-containing vaccines (e.g., DTaP, Tdap, DTP-Hib, DT, Td, TT)	A Anaphylaxis or anaphylactic shock	0-4 hours
	B Brachial neuritis	2-28 days
	C Any acute complication or sequela (including death) of above events	Not applicable
II Pertussis antigen-containing vaccines (e.g., DTaP, Tdap, DTP, P, DTP-Hib)	A Anaphylaxis or anaphylactic shock	0-4 hours
	B Encephalopathy (or encephalitis)	0-72 hours
	C Any acute complication or sequela (including death) of above events	Not applicable
III Measles, mumps and rubella virus-containing vaccines in any combination (e.g., MMR, MR, M, R)	A Anaphylaxis or anaphylactic shock	0-4 hours
	B Encephalopathy (or encephalitis)	5-15 days
	C Any acute complication or sequela (including death) of above events	Not applicable
IV Rubella virus-containing vaccines (e.g., MMR, MR, R)	A Chronic arthritis	7-42 days
	B Any acute complication or sequela (including death) of above event	Not applicable
V Measles virus-containing vaccines (e.g., MMR, MR, M)	A Thrombocytopenic purpura	7-30 days
	B Vaccine-Strain Measles Viral Infection in an immunodeficient recipient	0-6 months
	C Any acute complication or sequela (including death) of above events	Not applicable
VI Polio live virus-containing vaccines (OPV)	A Paralytic polio	
	- in a non-immunodeficient recipient	0-30 days
	- in an immunodeficient recipient	0-6 months
	- in a vaccine assoc. community case	Not applicable
	B Vaccine-strain polio viral infection	
	- in a non-immunodeficient recipient	0-30 days
	- in an immunodeficient recipient	0-6 months
	- in a vaccine assoc. community case	Not applicable
	C Any acute complication or sequela (including death) of above events	Not applicable
VII Polio inactivated-virus containing vaccines (e.g., IPV)	A Anaphylaxis or anaphylactic shock	0-4 hours
	B Any acute complication or sequela (including death) of above event	Not applicable
VIII Hepatitis B antigen-containing vaccines	A Anaphylaxis or anaphylactic shock	0-4 hours
	B Any acute complication or sequela (including death) of above event	Not applicable
IX *Haemophilus influenzae* type b polysaccharide conjugate vaccines	A No condition specified for compensation	Not applicable
X Varicella vaccine	A No condition specified for compensation	Not applicable
XI Rotavirus vaccine	A No condition specified for compensation	Not applicable
XII Vaccines containing live, oral, rhesus-based rotavirus	A Intussusception	0-30 days
	B Any acute complication or sequela (including death) of above event	Not applicable
XIII Pneumococcal conjugate vaccines	A No condition specified for compensation	Not applicable
XIV Any new vaccine recommended by the Centers for Disease Control and Prevention for routine administration to children, after publication by Secretary, HHS of a notice of coverage[b,c]	A No condition specified for compensation	Not applicable

[a] Effective date: February 1, 2007

[b] As of **December 1, 2004**, hepatitis A vaccines have been added to the Vaccine Injury Table (Table) under this Category. As of **July 1, 2005**, *trivalent* influenza vaccines have been added to the Table under this Category. Trivalent influenza vaccines are given annually during the flu season either by needle and syringe or in a nasal spray. All influenza vaccines routinely administered in the U.S. are trivalent vaccines covered under this Category.

[c] As of **February 1, 2007**, meningococcal (conjugate and polysaccharide) and human papillomavirus (HPV) vaccines have been added to the Table under this category.

See *News* on the VICP website for more information (www.hrsa.gov/vaccinecompensation).

Appendix F

Qualifications and Aids to Interpretation

(1) **Anaphylaxis and anaphylactic shock** mean an acute, severe, and potentially lethal systemic allergic reaction. Most cases resolve without sequelae. Signs and symptoms begin minutes to a few hours after exposure. Death, if it occurs, usually results from airway obstruction caused by laryngeal edema or bronchospasm and may be associated with cardiovascular collapse. Other significant clinical signs and symptoms may include the following: Cyanosis, hypotension, bradycardia, tachycardia, arrhythmia, edema of the pharynx and/or trachea and/or larynx with stridor and dyspnea. Autopsy findings may include acute emphysema which results from lower respiratory tract obstruction, edema of the hypopharynx, epiglottis, larynx, or trachea and minimal findings of eosinophilia in the liver, spleen and lungs. When death occurs within minutes of exposure and with out signs of respiratory distress, there may not be significant pathologic findings.

(2) **Encephalopathy**. For purposes of the Vaccine Injury Table, a vaccine recipient shall be considered to have suffered an encephalopathy only if such recipient manifests, within the applicable period, an injury meeting the description below of an acute encephalopathy, and then a chronic encephalopathy persists in such person for more than 6 months beyond the date of vaccination.

(i) An acute encephalopathy is one that is sufficiently severe so as to require hospitalization (whether or not hospitalization occurred).

(A) For children less than 18 months of age who present without an associated seizure event, an acute encephalopathy is indicated by a "significantly decreased level of consciousness" (see "D" below) lasting for at least 24 hours. Those children less than 18 months of age who present following a seizure shall be viewed as having an acute encephalopathy if their significantly decreased level of consciousness persists beyond 24 hours and cannot be attributed to a postictal state (seizure) or medication.

(B) For adults and children 18 months of age or older, an acute encephalopathy is one that persists for at least 24 hours and characterized by at least two of the following:

(1) A significant change in mental status that is not medication related; specifically a confusional state, or a delirium, or a psychosis;
(2) A significantly decreased level of consciousness, which is independent of a seizure and cannot be attributed to the effects of medication; and
(3) A seizure associated with loss of consciousness.

(C) Increased intracranial pressure may be a clinical feature of acute encephalopathy in any age group.

(D) A "significantly decreased level of consciousness" is indicated by the presence of at least one of the following clinical signs for at least 24 hours or greater (see paragraphs (2)(I)(A) and (2)(I)(B) of this section for applicable timeframes):

(1) Decreased or absent response to environment (responds, if at all, only to loud voice or painful stimuli);
(2) Decreased or absent eye contact (does not fix gaze upon family members or other individuals); or
(3) Inconsistent or absent responses to external stimuli (does not recognize familiar people or things).

(E) The following clinical features alone, or in combination, do not demonstrate an acute encephalopathy or a significant change in either mental status or level of consciousness as described above: Sleepiness, irritability (fussiness), high-pitched and unusual screaming, persistent inconsolable crying, and bulging fontanelle. Seizures in themselves are not sufficient to constitute a diagnosis of encephalopathy. In the absence of other evidence of an acute encephalopathy, seizures shall not be viewed as the first symptom or manifestation of the onset of an acute encephalopathy.

(ii) Chronic encephalopathy occurs when a change in mental or neurologic status, first manifested during the applicable time period, persists for a period of at least 6 months from the date of vaccination. Individuals who

return to a normal neurologic state after the acute encephalopathy shall not be presumed to have suffered residual neurologic damage from that event; any subsequent chronic encephalopathy shall not be presumed to be a sequela of the acute encephalopathy. If a preponderance of the evidence indicates that a child's chronic encephalopathy is secondary to genetic, prenatal or perinatal factors, that chronic encephalopathy shall not be considered to be a condition set forth in the Table.

(iii) An encephalopathy shall not be considered to be a condition set forth in the Table if in a proceeding on a petition, it is shown by a preponderance of the evidence that the encephalopathy was caused by an infection, a toxin, a metabolic disturbance, a structural lesion, a genetic disorder or trauma (without regard to whether the cause of the infection, toxin, trauma, metabolic disturbance, structural lesion or genetic disorder is known). If at the time a decision is made on a petition filed under section 2111(b) of the Act for a vaccine-related injury or death, it is not possible to determine the cause by a preponderance of the evidence of an encephalopathy, the encephalopathy shall be considered to be a condition set forth in the Table.

(iv) In determining whether or not an encephalopathy is a condition set forth in the Table, the Court shall consider the entire medical record.

3) **Seizure and convulsion**. For purposes of paragraphs (b)(2) of this section, the terms, "seizure" and "convulsion" include myoclonic, generalized tonic-clonic (grand mal), and simple and complex partial seizures. Absence (petit mal) seizures shall not be considered to be a condition set forth in the Table. Jerking move- ments or staring episodes alone are not necessarily an indication of seizure activity.

(4) **Sequela**. The term "sequela" means a condition or event which was actually caused by a condition listed in the Vaccine Injury Table.

(5) **Chronic Arthritis**. For purposes of the Vaccine Injury Table, chronic arthritis may be found in a person with no history in the 3 years prior to vaccination of arthropathy (joint disease) on the basis of:

(A) Medical documentation, recorded within 30 days after the onset, of objective signs of acute arthritis (joint swelling) that occurred between 7 and 42 days after a rubella vaccination;
(B) Medical documentation (recorded within 3 years after the onset of acute arthritis) of the persistence of objective signs of intermittent or continuous arthritis for more than 6 months following vaccination:
(C) Medical documentation of an antibody response to the rubella virus.

For purposes of the Vaccine Injury Table, the following shall not be considered as chronic arthritis: Musculoskeletal disorders such as diffuse connective tissue diseases (including but not limited to rheumatoid arthritis, juvenile rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, mixed connective tissue disease, polymyositis/ dermatomyositis, fibromyalgia, necrotizing vasculitis and vasculopathies and Sjogren's Syndrome), degenerative joint disease, infectious agents other than rubella (whether by direct invasion or as an immune reaction), metabolic and endocrine diseases, trauma, neoplasms, neuropathic disorders, bone and cartilage disorders and arthritis associated with ankylosing spondylitis, psoriasis, inflammatory bowel disease, Reiter's syndrome, or blood disorders. Arthralgia (joint pain) or stiffness without joint swelling shall not be viewed as chronic arthritis for \purposes of the Vaccine Injury Table.

(6) **Brachial neuritis** is defined as dysfunction limited to the upper extremity nerve plexus (i.e., its trunks, divisions, or cords) without involvement of other peripheral (e.g., nerve roots or a single peripheral nerve) or central (e.g., spinal cord) nervous system structures. A deep, steady, often severe aching pain in the shoulder and upper arm usually heralds onset of the condition. The pain is followed in days or weeks by weakness and atrophy in upper extremity muscle groups. Sensory loss may accompany the motor deficits, but is generally a less notable clinical feature. The neuritis, or plexopathy, may be present on the same side as or the opposite side of the injection; it is sometimes bilateral, affecting both upper extremities. Weakness is required before the diagnosis can be made. Motor, sensory, and reflex findings on physical examination and the results of nerve conduction and electromyographic studies must be consistent in confirming that dysfunction is attributable to the brachial plexus. The condition should thereby be distinguishable from conditions that may give rise to dysfunction of nerve roots (i.e., radiculopathies) and peripheral nerves (i.e., including multiple mononeuropathies), as well as other peripheral and central nervous system structures (e.g., cranial neuropathies and myelopathies).

(7) **Thrombocytopenic purpura** is defined by a serum platelet count less than 50,000/mm^3. Thrombocytopenic purpura does not include cases of thrombocytopenia associated with other causes such as hypersplenism, autoimmune disorders (including alloantibodies from previous transfusions) myelodysplasias, lymphoproliferative disorders, congenital thrombocytopenia or hemolytic uremic syndrome. This does not include cases of immune (formerly called idiopathic) thrombocytopenic purpura (ITP) that are mediated, for example, by viral or fungal infections, toxins or drugs. Thrombocytopenic purpura does not include cases of thrombocytopenia associated with disseminated intravascular coagulation, as observed with bacterial and viral infections. Viral infections include, for example, those infections secondary to Epstein Barr virus, cytomegalovirus, hepatitis A and B, rhinovirus, human immunodeficiency virus (HIV), adenovirus, and dengue virus. An antecedent viral infection may be demonstrated by clinical signs and symptoms and need not be confirmed by culture or serologic testing. Bone marrow examination, if performed, must reveal a normal or an increased number of megakaryocytes in an otherwise normal marrow.

(8) **Vaccine-strain measles viral infection** is defined as a disease caused by the vaccine-strain that should be determined by vaccine specific monoclonal antibody or polymerase chain reaction tests.

(9) **Vaccine-strain polio viral infectio**n is defined as a disease caused by poliovirus that is isolated from the affected tissue and should be determined to be the vaccine-strain by oligonucleotide or polymerase chain reaction. Isolation of poliovirus from the stool is not sufficient to establish a tissue specific infection or disease caused by vaccine-strain poliovirus.

APPENDIX G
Data and Statistics

Reported Cases and Deaths from Vaccine-Preventable Diseases: 1950-2008* **G-1**

Impact of Vaccines in the 20th & 21st Centuries **G-7**

Vaccine Coverage Levels: 1962-2007 . . . . . **G-8**

*Provisional

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Reported Cases and Deaths from Vaccine Preventable Diseases, United States, 1950-2008*

	Diphtheria		Tetanus		Pertussis		Polio (paralytic)	
Year	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
1950	5,796	410	486	336	120,718	1,118	33,300	1,904
1951	3,983	302	506	394	68,687	951	28,386	1,551
1952	2,960	217	484	360	45,030	402	57,879	3,145
1953	2,355	156	506	337	37,129	270	35,592	1,450
1954	2,041	145	524	332	60,886	373	38,476	1,368
1955	1,984	150	462	265	62,786	467	28,985	1043
1956	1,568	103	468	246	31,732	266	15,140	566
1957	1,211	81	447	279	28,295	183	5,485	221
1958	918	74	445	303	32,148	177	5,787	255
1959	934	72	445	283	40,005	269	8,425	454
1960	918	69	368	231	14,809	118	3,190	230
1960	617	68	379	242	11,468	76	1,312	90
1962	444	41	322	215	17,749	83	910	60
1963	314	45	325	210	17,135	115	449	41
1964	293	42	289	179	13,005	93	122	17
1965	164	18	300	181	6,799	55	72	16
1966	209	20	235	158	7,717	49	113	9
1967	219	32	263	144	9,718	37	41	16
1968	260	30	178	66	4,810	36	53	24
1969	241	25	192	89	3,285	13	20	13
1970	435	30	148	79	4,249	12	33	7
1971	215	13	116	64	3036	18	21	18
1972	152	10	128	58	3,287	6	31	2
1973	228	10	101	40	1,759	5	8	10
1974	272	5	101	44	2,402	14	7	3
1975	307	5	102	45	1,738	8	13	9
1976	128	7	75	32	1,010	7	10	16
1977	84	5	87	24	2,177	10	19	16
1978	76	4	86	32	2,063	6	8	13

*2008 provisional data. *MMWR* 2009;57(No. 53): 1420-31.

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	Diphtheria		Tetanus		Pertussis		Polio (paralytic)	
Year	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
1979	59	1	81	30	1,623	6	22	1
1980	3	1	95	28	1,730	11	9	2
1981	5	0	72	31	1,248	6	10	0
1982	2	1	88	22	1,895	4	12	0
1983	5	0	91	22	2,463	5	13	0
1984	1	0	74	20	2,276	7	9	0
1985	3	0	83	23	3,589	4	8	0
1986	0	0	64	22	4,195	6	10	0
1987	3	1	48	16	2,823	1	9	0
1988	2	0	53	17	3,450	4	9	0
1989	3	0	53	9	4,157	12	10	0
1990	4	1	64	11	4,570	12	6	0
1991	5	0	57	11	2,719	0	9	1
1992	4	1	45	9	4,083	5	6	0
1993	0	0	48	11	6,586	1	3	0
1994	2	0	51	9	4,617	8	8	0
1995	0	1	41	5	5,137	6	6	1
1996	2	0	36	1	7,796	4	7	0
1997	4	0	50	4	6,564	6	7	0
1998	1	1	34	7	6,279	5	2	0
1999	1	1	40	7	7,288	7	2	0
2000	1	0	35	5	7,867	12	0	0
2001	2	0	37	5	7,580	17	0	0
2002	1	0	25	5	9,771	18	0	0
2003	1	1	20	4	11,647	11	0	0
2004	0	0	34	4	25,827	16	0	0
2005	0	0	27	1	25,616	31	1**	0
2006	0	0	41	NA	15,632	NA	0	0
2007	0	0	28	NA	10,454	NA	0	0
2008*	0	0	15	NA	10,007	NA	0	0

**Vaccine-associated polio acquired outside the United States

	Measles		Mumps		Rubella		CRS
Year	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases
1950	319,124	468	NR		NR		NR
1951	530,118	683	NR		NR		NR
1952	683,077	618	NR		NR		NR
1953	449,146	462	NR		NR		NR
1954	682,720	518	NR		NR		NR
1955	555,156	345	NR		NR		NR
1956	611,936	530	NR		NR		NR
1957	486,799	389	NR		NR		NR
1958	763,094	552	NR		NR		NR
1959	406,162	385	NR		NR		NR
1960	441,703	380	NR	42	NR	12	NR
1961	423,919	434	NR	53	NR	14	NR
1962	481,530	408	NR	43	NR	8	NR
1963	385,156	364	NR	48	NR	16	NR
1964	458,083	421	NR	50	NR	53	NR
1965	261,904	276	NR	31	NR	16	NR
1966	204,136	261	NR	43	46,975	12	NR
1967	62,705	81	NR	37	46,888	16	NR
1968	22,231	24	152,209	25	49,371	24	NR
1969	25,826	41	90,918	22	57,686	29	62
1970	47,351	89	104,953	16	56,552	31	67
1971	75,290	90	124,939	22	45,086	20	44
1972	32,275	24	74,215	16	25,507	14	32
1973	26,690	23	69,612	12	27,804	16	30
1974	22,094	20	59,128	6	11,917	15	22
1975	24,374	20	59,647	8	16,652	21	32
1976	41,126	12	38,492	8	12,491	12	22
1977	57,345	15	21,436	5	20,395	17	29
1978	26,871	11	16,817	3	18,269	10	30
1979	13,597	6	14,255	2	11,795	1	57
1980	13,506	11	8,576	2	3,904	1	14
1981	3,124	2	4,941	1	2,077	5	10

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	Measles		Mumps		Rubella		CRS
Year	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases
1982	1,714	2	5,270	2	2,325	4	13
1983	1,497	4	3,355	2	970	3	7
1984	2,587	1	3,021	1	752	1	2
1985	2,822	4	2,982	0	630	1	2
1986	6,282	2	7,790	0	55	1	13
1987	3,655	2	12,848	2	306	0	3
1988	3,396	3	4,866	2	225	1	2
1989	18,193	32	5,712	3	396	4	2
1990	27,786	64	5,292	1	1,125	8	32
1991	9,643	27	4,264	1	1,401	1	34
1992	2,237	4	2,572	0	160	1	11
1993	312	0	1,692	0	192	0	4
1994	963	0	1,537	0	227	0	7
1995	309	2	906	0	128	1	3
1996	508	1	751	1	238	0	2
1997	138	2	683	0	181	0	9
1998	100	0	666	1	364	0	9
1999	100	2	387	1	267	0	6
2000	86	1	338	2	176	0	8
2001	116	1	266	0	23	2	3
2002	44	0	270	1	18	0	1
2003	56	1	231	0	7	0	4
2004	37	0	258	0	10	1	0
2005	66	1	314	0	11	0	1
2006	55	NA	6,584	NA	11	NA	1
2007	43	NA	800	NA	12	NA	0
2008*	132	NA	396	NA	17	NA	0

	Hepatitis A		Hepatitis B		Haemophilus		Varicella	
Year	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
1966	32,859	NA	1,497	NA	NR	NR	NR	
1967	38,909	NA	2,458	NA	NR	NR	NR	
1968	45,893	NA	4,829	NA	NR	NR	NR	
1969	48,416	NA	5,909	NA	NR	NR	NR	
1970	56,797	NA	8,310	NA	NR	NR	NR	
1971	59,606	NA	9,556	NA	NR	NR	NR	
1972	54,074	NA	9,402	NA	NR	NR	164,114	122
1973	50,749	NA	8,451	NA	NR	NR	182,927	138
1974	40,358	NA	10,631	NA	NR	NR	141,495	106
1975	35,855	NA	13,121	NA	NR	NR	154,248	83
1976	33,288	NA	14,973	NA	NR	NR	183,990	106
1977	31,153	NA	16,831	NA	NR	NR	188,396	89
1978	29,500	NA	15,016	NA	NR	NR	154,089	91
1979	30,407	129	15,452	260	NR	NR	199,081	103
1980	29,087	112	19,015	294	NR	NR	190,894	78
1981	25,802	93	21,152	394	NR	NR	200,766	84
1982	23,403	83	22,177	375	NR	NR	167,423	61
1983	21,532	82	24,318	438	NR	NR	177,462	57
1984	22,040	77	26,115	465	NR	NR	221,983	53
1985	23,210	80	26,611	490	NR	NR	178,162	68
1986	23,430	65	26,107	557	NR	NR	183,243	47
1987	25,280	77	25,916	595	NR	NR	213,196	89
1988	28,507	70	23,177	621	NR	NR	192,857	83
1989	35,821	88	23,419	711	NR	NR	185,441	89
1990	31,441	76	21,102	816	NR	NR	173,099	120
1991	24,378	71	18,003	912	2,764	17	147,076	81
1992	23,112	82	16,126	903	1,412	16	158,364	100
1993	24,238	95	13,361	1041	1,419	7	134,722	100
1994	26,796	97	12,517	1120	1,174	5	151,219	124
1995	31,582	142	10,805	1027	1,180	12	120,624	115
1996	31,032	121	10,637	1082	1,170	7	83,511	81

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	Hepatitis A		Hepatitis B		Haemophilus		Varicella	
Year	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
1997	30,021	127	10,416	1,030	1,162	7	98,727	99
1998	23,229	114	10,258	1,052	1,194	11	82,455	81
1999	17,047	134	7,694	832	1,309	6	46,016	48
2000	13,397	106	8,036	886	1,398	6	27,382	44
2001	10,609	83	7,843	769	1,597	11	22,536	26
2002	8,795	76	7,996	762	1,743	7	22,841	32
2003	7,653	54	7,526	685	2,013	5	20,948	16
2004	5,970	58	6,741	643	2,085	11	26,659	19
2005	4,488	43	5,119	642	2,304	4	32,242	13
2006	3,579	NA	4,713	NA	2,436	NA	48,445	NA
2007	2,979	NA	4,519	NA	2,541	NA	40,146	NA
2008*	2,340	NA	3,513	NA	2,547	NA	26,924	NA

Notes

NA - Not Available
NR - Not nationally reportable
CRS: Congenital Rubella Syndrome

Prior to 1966, hepatitis A and B were not separated from other types of hepatitis. Prior to 1978, deaths from hepatitis A and B were not separated from deaths from other types of hepatitis.

Haemophilus (Hi) reporting includes all serotypes and all ages. In 2008, 27 cases of invasive Hi type B disease were reported among children <5 years of age.

Varicella was removed from the nationally notifiable disease list in 1991. In 2008, varicella cases were reported from 33 states, the District of Columbia, Guam, and Puerto Rico.

Sources:
Final totals for 2007: *MMWR* 2008;57(33):903-13.
Final totals for 2006: *MMWR* 2007;56(33):851-64.
Final totals for 2005: *MMWR* 2006;55(32):883-93.
Final totals for 2004: Summary of Notifiable Diseases, United States, 2004. *MMWR* 2006;53(53):18-19.
Reportable disease (1950-2003): Earlier editions of Summary of Notifiable Diseases, published annually in *MMWR*.

Deaths: National Center for Health Statistics Mortality Report for respective years.

March 2009

Impact of Vaccines in the 20th & 21st Centuries

Disease	20th Century Annual Morbidity	2007 Total	% Decrease
Smallpox	48,164	0	100
Diphtheria	175,885	0	100
Pertussis	147,271	10,454	93
Tetanus	1,314	28	98
Polio (paralytic)	16,316	0	100
Measles	503,282	43	>99.9
Mumps	152,209	800	99.5
Rubella	47,745	12	>99.9
Congenital rubella	823	0	100
Haemophilus influenzae (<5 years)	20,000 (est)	202 (serotype B or unknown serotype)	99

Sources:

1. CDC. Impact of vaccines universally recommended for children – United States, 1900-1998. *MMWR* 1999;48(12): 243-8

2. CDC. Notice to Readers: Final 2007 Reports of Notifiable Diseases. *MMWR* 2008;57(33):903-13

3/20/09

Appendix G

Vaccine Coverage Levels – United States, 1962-2007

Year	DTP3+	DTP4+	Polio3+	MMR*	Hib3+	Var	PCV3+	HepB3+	Combined 4-3-1	Combined 4-3-1-3
1962	67.3									
1963	71.4									
1964	74.6									
1965	72.7									
1966	74.0									
1967	77.9			60.0						
1968	76.8			61.5						
1969	77.4			61.4						
1970	76.4			58.4						
1971	77.8			62.2						
1972	74.1			62.8						
1973	71.7		59.5	61.0						
1974	72.4		60.0	63.4						
1975	73.2		63.6	65.5						
1976	72.7		61.3	66.3						
1977	69.6		62.6	65.0						
1978	66.6		59.5	63.6						
1979	64.4		59.7	66.5						
1980	66.0		58.9	66.6						
1981	68.1		59.2	66.8						
1982	67.1		57.0	67.6						
1983	65.4		56.9	66.3						
1984	65.0		53.2	65.8						
1985	63.6		53.6	61.2						
1986†										
1987†										
1988†										
1989†										

Year	DTP3+	DTP4+	Polio3+	MMR*	Hib3+	Var	PCV3+	HepB3+	Combined 4-3-1	Combined 4-3-1-3
1990†										
1991	68.8		53.2	82.0						
1992	83.0	59.0	72.4	82.5	28.2			8.0	68.7	55.3
1993	88.2	72.1	78.9	84.1	55.0			16.3	67.1	
1994	93.0	77.7	83.0	89.0	86.0			37.0	75.0	
1995	94.7	78.5	87.9	87.6	91.7			68.0	76.2	74.2
1996	95.0	81.1	91.1	90.7	91.7	16.0		81.8	78.4	76.5
1997	95.5	81.5	90.8	90.5	92.7	25.9		83.7	77.9	76.2
1998	95.6	83.9	90.8	92.0	93.4	43.2		87.0	80.6	79.2
1999	95.9	83.3	89.6	91.5	93.5	57.5		88.1	79.9	78.4
2000	94.1	81.7	89.5	90.5	93.4	67.8		90.3	77.6	76.2
2001	94.3	82.1	89.4	91.4	93.0	76.3		88.9	78.6	77.2
2002	94.9	81.6	90.2	91.6	93.1	80.6	40.8	89.9	78.5	77.5
2003	96.0	84.8	91.6	93.0	93.9	84.8	68.1	92.4	82.2	81.3
2004	95.9	85.5	91.6	93.0	93.5	87.5	73.2	92.4	83.5	82.5
2005	96.1	85.7	91.7	91.5	93.9	87.9	82.8	92.9	83.1	82.4
2006	95.8	85.2	92.9	92.4	93.4	89.3	87.0	93.4	83.2	82.3
2007	95.5	84.5	92.6	92.3	92.6	90.0	90.0	92.7	82.8	81.1

*Previously reported as measles-containing vaccine (MCV).
†No national coverage data were collected from 1986 through 1990.

Var: varicella vaccine

Combined 4-3-1: Four or more doses of DTP/DTaP/DT, three or more doses of poliovirus vaccine, and one or more doses of any measles-containing vaccine.

Combined 4-3-1-3: Four or more doses of DTP/DTaP/DT, three or more doses of poliovirus vaccine, one or more doses of any measles-containing vaccine, and three or more doses of *Haemophilus influenzae* type b vaccine.

Data prior to 1993 were collected by the National Health Interview Survey and represent 2-year-old children. Data from 1993 are from the National Immunization Survey and represent 19-35 month-old children. Different methods were used for the two surveys.

Most recent publication: CDC. National, State, and Local Area Vaccination Coverage Among Children Aged 19-35 Months – United States, 2007. *MMWR* 2008;57(35);961-66.

APPENDIX H
Immunization Resources

CDC Immunization Contacts & Resources H-1

IAC Online Directory of Immunization Resources H-2

Sample IAC Print Materials H-3

IAC Express Information Sheet H-4

"Immunization Techniques" Video H-5

"Storage and Handling Toolkit" H-6

State and Local Immunization Grantee Contact Information H-7

Appendix H

Centers for Disease Control and Prevention
and
National Center for Immunization & Respiratory Diseases (NCIRD)

Contact Information & Resources

Telephone

Immunization Call Center

800-232-4636 (800-CDC-INFO)

Contact CDC-INFO 24 hours a day, 7 days a week, in English or Spanish, with questions concerning immunizations or vaccine-preventable diseases, to find the location of immunization clinics near you, or to order single copies of immunization materials from NCIRD.

E-Mail

nipinfo@cdc.gov

Healthcare providers can send their immunization or vaccine-preventable disease related questions to this e-mail address. You will get an answer from a CDC immunization expert, usually within 24 hours.

Internet

NCIRD: http://www.cdc.gov/vaccines
Vaccine Safety: http://www.cdc.gov/od/science/iso or
http://www.cdc.gov/vaccines/vac-gen/safety/default.htm
Hepatitis: http://www.cdc.gov/hepatitis
Influenza: http://www.cdc.gov/flu
Travelers' Health: http://wwwn.cdc.gov/travel

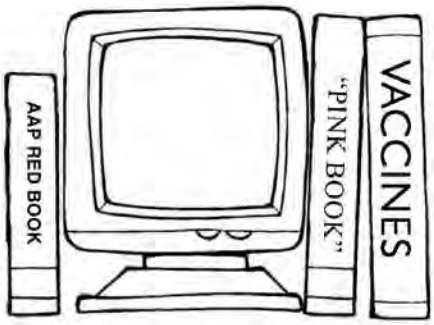
Calendar of upcoming events, online access to publications such as ACIP statements and Vaccine Information Statements, online publications ordering, vaccine safety information, latest pediatric and adult immunization schedules, downloadable Clinic Assessment Software Application (CASA), Frequently Asked Questions, PowerPoint slide presentations, links to other immunization sites, and much more.

NCIRD Training & Education Resources. Download NCIRD's curriculum brochure:
http://www.cdc.gov/vaccines/ed/curric-brochure.htm

Publications may be ordered through NCIRD's online order form:
http://www.cdc.gov/vaccines/pubs/default.htm

IAC's Online Directory of Immunization Resources

Visit our website to find the Immunization Action Coalition's online directory of immunization resources. Continually updated, it keeps you in the know about immunization and viral hepatitis issues and resources. Use it to gain access to hundreds of reliable sources of information with the click of a mouse. Here's what you'll find:



- **Books and Periodicals:** Standard resources for providers, as well as helpful and informative books for patients and parents.
- **CDC Materials:** Ordering information for CDC-produced materials; links to frequently requested items, live satellite broadcasts, and websites; and a listing of telephone and email information services.
- **Continuing Educational Opportunities for Health Professionals:** Listings and links for providers needing CMEs, CNEs, CEUs, or just to stay current.
- **Email News Services:** Information about how to sign up to receive periodic email updates from several immunization-related organizations.
- **Government Agencies:** Links to most federal agencies (e.g., CDC, FDA) and state health departments.
- **Hotlines:** Information about toll-free hotlines for providers and patients.
- **IAC Materials:** Links to IAC's ready-to-print educational pieces for providers, patients, and parents—and much more.

Visit us:

www.immunize.org/resources

- **International Organizations:** Links to organizations (e.g., WHO, PAHO, GAVI) providing information on international immunization and hepatitis issues.
- **Other Immunization Partners:** Links to other organizations and professional societies that provide immunization information.
- **Videos and More:** Helpful videos, DVDs, and other electronic formats for providers, patients, and parents to learn more about immunization and viral hepatitis.

To get free weekly updates on new immunization resources, subscribe to IAC's news service, IAC Express, at www.immunize.org/subscribe

www.immunize.org/news.d/6012resr.pdf • Item #U6012 (1/07)

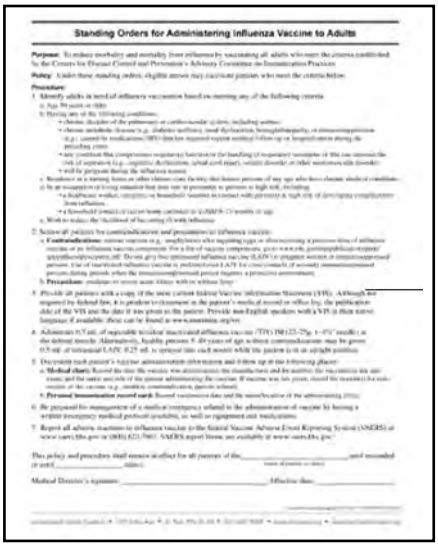
Immunization Action Coalition • 1573 Selby Ave. • St. Paul, MN 55104 • (651) 647-9009 • www.immunize.org • www.vaccineinformation.org

Sample IAC Print Materials

These, and many other useful materials for both providers and patients, can be downloaded free of charge from the IAC's website at http://www.immunize.org/catg.d/free.htm



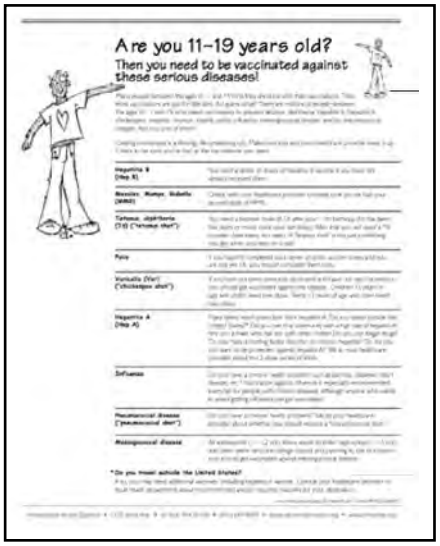
Vaccine AdministrationRecord
for Children and Teens
http://www.immunize.org/catg.d/p2022b.pdf



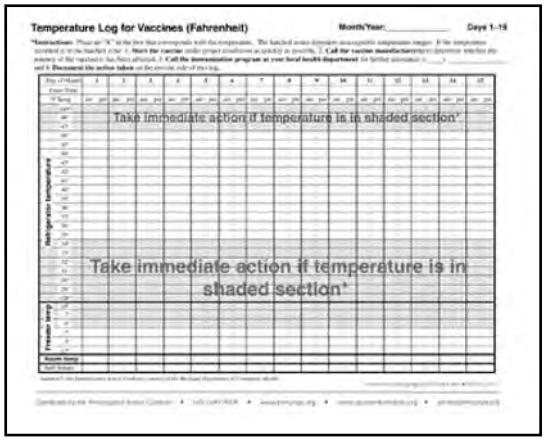
Standing Orders for Administering
Influenza Vaccine to Adults
http://www.immunize.org/catg.d/p3074.pdf



Screening Questionnaire
for Child and Teen Immunization
http://www.immunize.org/catg.d/p4060.pdf



Are You 11-19 Years Old?
http://www.immunize.org/catg.d/11teens8.pdf



Temperature Log for Vaccines (Fahrenheit)
http://www.immunize.org/catg.d/p3039pdf



"Handy" resources



Practical information about immunization and vaccine-preventable diseases

Subscribe to IAC's FREE publications

It's so easy to subscribe to IAC's 3 print periodicals—
Needle Tips, Vaccinate Adults, and *Vaccinate Women*—
and email news service *IAC Express.*
Just go to www.immunize.org/subscribe, follow the directions,
and you're done!

Visit www.immunize.org

Hundreds of free, ready-to-copy immunization and viral hepatitis print materials for your patients and staff and many other free resources, including VISs in more than 30 languages

Visit www.vaccineinformation.org

Disease and vaccine information for the public
and healthcare professionals (photos & videos, too!)

www.immunize.org/news.d/u6005.pdf • Item #U6005 (8/08)

Immunization Action Coalition • 1573 Selby Ave. • St. Paul, MN 55104 • (651) 647-9009 • www.immunize.org • www.vaccineinformation.org

DVD: Immunization Techniques "Safe, Effective, Caring" [VHS version]



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for credit cards only

View Cart

Order Form
for all payment types

The video "Immunization Techniques: Safe, Effective, Caring" is now available on DVD. Every clinic in the United States that delivers vaccination services should have a copy of this 35-minute video available for clinic staff. This video teaches best practices about how to administer intramuscular (IM) and subcutaneous (SC) vaccines to infants, children, and adults. It is designed for use as a "hands-on" instructional program for new staff as well as a refresher course for experienced health professionals.

The DVD provides discussion of all the following:
- Anatomic sites
- Choice of needle size
- Vaccines and routes of administration
- Demonstrations of infants, toddlers, kindergartners, and adults being vaccinated
- How to "draw up" doses of vaccine

Features
- 35-minute DVD on immunization techniques
- English and dubbed-Spanish versions

The DVD disk includes English- and Spanish-language versions of the following print materials
- Presenter's notes
- "Comforting Restraint," a poster that clearly shows parents how to hold a child during vaccination
- "Be there for your child," a poster that presents ideas parents can use before, during, and after vaccination to make the experience easier for their child.

The DVD also includes the following print materials in English only:
- Skills checklist to help you document that your staff is well trained.
- "Immunization Record and History," a chart that allows health professionals to document vaccine administration information for each of the recommended childhood vaccines
- A resource list that directs parents to sources of reliable immunization information

New price effective October 1, 2007: $10.50 each

For quotes on larger quantities, call 651-647-9009 or email admininfo@immunize.org

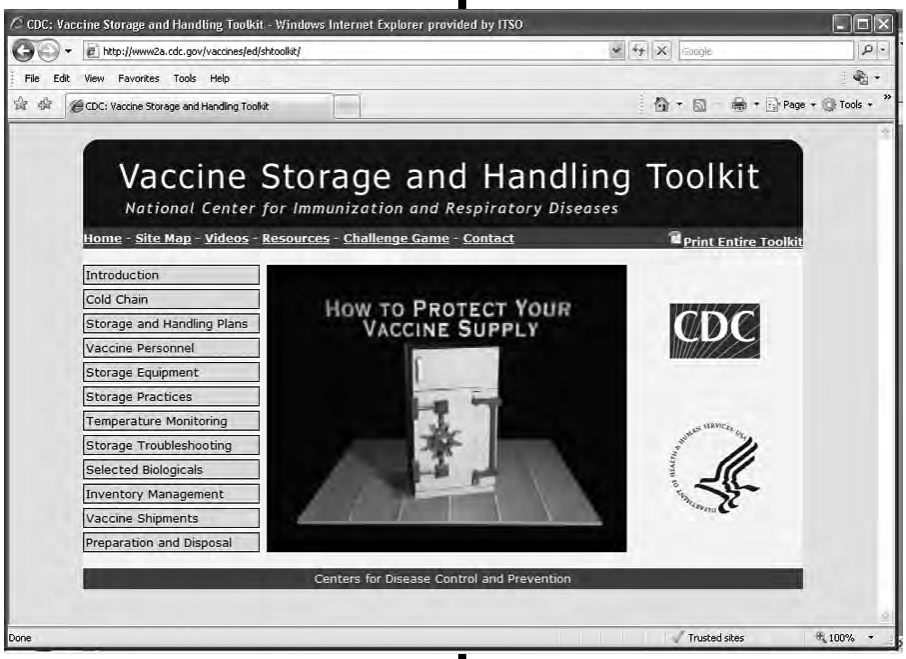
Developed by the California Department of Health Services Immunization Branch in collaboration with a team of national experts

http://www.immunize.org/shop/toolkit_iztechdvd.asp

Vaccine Storage and Handling Toolkit

Everything you want to know about vaccine storage and handling in one place!

- Forms
- Posters
- Checklists
- Interactive Game
- Videos
- Storage & Handling Guidelines
- Contact Information



Online at www2a.cdc.gov/vaccines/ed/shtoolkit

National Center for Immunization and Respiratory Diseases
IMMUNIZATION GRANTEES
March 19, 2009
(see http://www2a.cdc.gov/nip/progmgr/fieldstaff.asp?rpt=pm for updated list)

STATE & CITY GRANTEES

ALABAMA
Alabama Department of Public Health
State Immunization Program
P.O. Box 303017
Montgomery, AL 36130-3017

PHONE #: (334) 206-5023
FAX #: (334) 206-2044
Program Manager: Winkler Sims
Email: wsims@adph.state.al.us

Fed Ex: Disease Control/Immunization Div.
The RSA Tower
201 Monroe St., Suite 1460
Montgomery, AL 36104

ALASKA
Alaska Department of Health and Social Services
Immunization Program
3601 C. Street, Suite 540
P.O. Box 240249
Anchorage, Alaska 99503

PHONE #: (907) 269-8000
FAX #: (907) 562-7802
Program Manager: Laurel H. Wood
Email: laurel_wood@health.state.ak.us

ARIZONA
Arizona Department of Health Services
Immunization Program Office
150 N. 18th Ave.
Phoenix, Arizona 85007-3233

PHONE #: (602) 364-3630
FAX #: (602)364-3276
Program Manager: Patty Gast
Email: gastp@azdhs.gov

ARKANSAS
Arkansas Department of Health
Immunization Program
4815 West Markham
Slot #48
Little Rock, Arkansas 72205-3867

PHONE #: (501) 661-2000
FAX #: (501) 661-2300
Program Manager: Karen Fowler
Email: Karen.Fowler@Arkansas.gov

CALIFORNIA
California Department of Health Svcs
Immunization Branch
850 Marina Bay Parkway, Building P
Richmond, California 94804-6403

PHONE #: (510) 540-2065
FAX #: (510) 883-6015
Program Manager: Robert Schechter
Email: Robert.schechter@cdph.ca.gov

COLORADO
Colorado Department of Public Health & Environment
PSD-IMM-A4
4300 Cherry Creek Dr., South
Denver, Colorado 80246-1530

PHONE #: (303) 692-2650
FAX #: (303) 691-6118
Program Manager: Joni Reynolds
Email: Joni.Reynolds@state.co.us

CONNECTICUT
Connecticut State Dept of Public Health
Immunization Program
P.O. Box 340308
410 Capitol Avenue, MS# 11 MUN
Hartford, Connecticut 06134-0308

PHONE #: (860) 509-7929
FAX #: (860) 509-7945
ProgramManager: Vincent Sacco
Email: vincent.sacco@ct.gov

DELAWARE
Immunization Program/Div of Public Health
Delaware Dept of Health & Social Services
Blue Hen Corporate Center
655 South Bay Rd, Suite 218, Room 111
Dover, Delaware 19901

PHONE #: (302) 741-2940
FAX #: (302) 739-2358
ProgramManager: Mayra Lacen
Email: mayra.Lacen@state.de.us

FLORIDA
Florida Department of Health
Bureau of Immunization
4052 Bald Cypress Way, #A-11
Tallahassee, Florida 32399-1719
Fed Ex: 2585 Merchants Row Blvd, Rm 210
Prather Bldg, Suite 210
Tallahassee, FL 32399-1719

PHONE #: (850) 245-4342
FAX #: (850) 922-4195
Program Manager: Charles Alexander
Email: charles_alexander@doh.state.fl.us

GEORGIA
Georgia Department of Human Resources
Division of Public Health
Two Peachtree Street, N.W., Suite 13-476
Atlanta, Georgia 30303

PHONE #: (404) 657-3158
FAX #: (404) 657-1463
Program Manager: Michelle Conner
Email: mmconner@dhr.state.ga.us

HAWAII
Hawaii Department of Health
Immunization Program
1250 Punchbowl Street - Room 428
P.O. Box 3378
Honolulu, Hawaii 96801
Fed Ex: 1250 Punchbowl St., Rm 428
Honolulu, Hawaii 96813

PHONE #: (808) 586-8300
FAX #: (808) 586-8302
Program Manager: Lisa Mendez
Email: lisa.mendez@doh.hawaii.gov

IDAHO
Idaho Department of Health and Welfare
Immunization Program
4th Floor, 450 West State Street
Boise, Idaho 83270

PHONE #: (208) 334-5931
FAX #: (208) 334-4914
Program Manager: Rebecca Coyle
Email: coyler@dhw.idaho.gov

ILLINOIS
Ilinois Department of Public Health
Immunization Program
525 West Jefferson Street
Springfield, Illinois 62761

PHONE #: (217) 785-1455
FAX #: (217) 524-0967
Program Manager: Karen McMahon
Email: Karen.McMahon@illinois.gov

CHICAGO
Chicago Department of Health
Immunization Program
Westside Center for Disease Control
2160 West Ogden Avenue
Chicago, Illinois 60612

PHONE #: (312) 746-5380
FAX #: (312) 746-6388
Program Manager: Julie Morita
Email: morita_julie@cdph.org

INDIANA
Indiana State Department of Health
Immunization Program
2 North Meridian Street
Indianapolis, Indiana 46204-3003

PHONE #: (800) 701-0704
FAX #: (317) 233-7805
Program Manager: Amanda Mizell
Email: amizell@isdh.IN.gov

IOWA
Iowa Department of Public Health
Division of Family/Community Health
321 E. 12th Street
Des Moines, Iowa 50319-0075

PHONE #: (515) 281-4923
FAX #: (800) 831-6292
Program Manager: Don Callaghan
Email: dcallagh@idph.state.ia.us

KANSAS
Kansas State Department of Health
Bureau of Disease Prevention
900 S.W. Jackson Street
L.S.O.B Suite 901 N
Topeka, Kansas 66612-1274

PHONE #: (785) 296-5591
FAX #: (785) 296-6368
Program Manager: Sue Bowden
Email: sbowden@kdhe.state.ks.us

KENTUCKY
Kentucky Department for Public Health
Immunization Program
275 East Main Street, HSIC-D
Frankfort, Kentucky 40621-0001

PHONE #: (502) 564-4478
FAX #: (502) 564-4760
Program Manager: David Miller
Email: Dave.Miller@ky.gov

LOUISIANA
Louisiana Office of Public Health
Immunization Program - Suite 107
1450 L and A Road
Metairie, Louisiana 70001

PHONE #: (504) 838-5300
FAX #: (504) 483-1909
Program Manager: Ruben Tapia
Email: Ruben.tapia@la.gov

MAINE
Maine Department of Human Services
Immunization Program
2 Bangor Street
11 State House Station
Augusta, Maine 04333

PHONE #: (207) 287-3746
FAX #: (207) 287-8127
Program Manager: Jiancheng Huang
Email: jiancheng.haung@maine.gov

MARYLAND
Maryland Department of Health & Mental Hygiene
Center for Immunization
201 West Preston Street, 3rd Floor
Baltimore, Maryland 21201

PHONE #: (410) 767-6679
FAX #: (410) 333-5893
Program Manager: Gregory Reed
Email: reedgre@dhmh.state.md.us

MASSACHUSETTS
Massachusetts State Lab Inst - CDC
Division of Epidemiology & Immunization
305 South Street, Room 506B
Jamaica Plain, Massachusetts 02130-3597

PHONE #: (617) 983-6800
FAX #: (617) 983-6868
Program Manager: Susan Lett
Email: susan.lett@state.ma.us

MICHIGAN
Michigan Department of Community Health
Division of Immunization
201 Townsend Street
P.O. Box 30195
Lansing, Michigan 48909

PHONE #: (517) 335-8159
FAX #: (517) 335-9855
Program Manager: Bob Swanson
Email: SwansonR@michigan.gov

MINNESOTA
Minnesota Department of Health
Immunization Program
625 N. Roberts Street
P.O. Box 64975
St. Paul, Minnesota 55164-0975

PHONE #: (612) 676-5100
FAX #: (612) 676-5689
Program Manager: Margo Roddy
Email: Margaret.Roddy@health.state.mn.us

MISSISSIPPI
Mississippi State Department of Health
Division of Immunization
570 Woodrow Wilson Blvd
P.O. Box 1700
Jackson, Mississippi 39215-1700

PHONE #: (601) 576-7751
FAX #: (601) 576-7686
Program Manager: Regina Irvin
Email: rirvin@msdh.state.ms.us

MISSOURI
Missouri Department of Health
Section of Vaccine-Preventable Diseases
930 Wildwood Drive
P.O. Box 570
Jefferson City, Missouri 65102

PHONE #: (573) 751-6439
FAX #: (573) 526-6892
Program Manager: Jeannie Ruth
Email: jeannie.ruth@dhss.mo.gov

MONTANA
Montana Department of Health & Human Svcs
Health Policy and Services Div
Cogswell Building - Room C211
P.O. Box 202951
Helena, Montana 59620

PHONE #: (406) 444-5580
FAX #: (406) 444-2920
Program Manager: Liz LeLacheur
Email: elelacheur@mt.gov

NEBRASKA
Nebraska Department of Health & Human Services
Immunization Program
301 Centennial Mall South
P.O. Box 95007
Lincoln, Nebraska 68509-5007

PHONE #: (402) 471-6423
FAX #: (402) 471-6426
Program Manager: Barbara Ludwig
Email: barbara.ludwig@dhhs.ne.gov

NEVADA
Nevada State Health Division
Immunization Program
505 King Street, Room 103
Carson City, Nevada 89701

PHONE #: (775) 684-5900
FAX #: (775) 684-8338
Program Manager: Tami Chartraw
Email: tchartraw@health.nv.gov

NEW HAMPSHIRE
New Hampshire Department of Health & Human Svcs
Immunization Program
Six Hazen Drive
Concord, New Hampshire 03301

PHONE #: (603) 271-4482
FAX #: (603) 271-3850
Program Manager: Marcella Bobinsky
Email: mbobinsky@dhhs.state.nh.us

NEW JERSEY
New Jersey State Department of Health & Senior Svcs
Immunization Program
P.O. Box 369
Trenton, New Jersey 08625-0369
Fed Ex: 3635 Quaker Bridge Road
Mercerville, NJ 08619-9998

PHONE #: (609) 588-7520
FAX #: (609) 588-7431
Program Manager: Angela Sorrells
Email: Angela.Sorrells@doh.state.nj.us

NEW MEXICO
New Mexico Department of Health
Immunization Program
1190 St. Francis Drive
Rennels Building - Suite 1261
Santa Fe, New Mexico 87502

PHONE #: (505) 827-2369
FAX #: (505) 827-2898
Program Manager: Gayle Kenny
Email: gayle.kenny@state.nm.us

NEW YORK
New York State Department of Health
Immunization Program
Corning Tower Building
Room 649
Albany, New York 12237-0627

PHONE #: (518) 473-4437
FAX #: (518) 474-7381
Program Manager: David Lynch
Email: DRL05@health.state.ny.us

NEW YORK CITY
New York City Department of Health
Bureau of Immunization
2 Lafayette Street - 19th Floor
New York, New York 10007

PHONE #: (212) 676-2259
FAX #: (212) 676-2252
Program Manager: Jane Zucker
Email: jzucker@health.nyc.gov

NORTH CAROLINA
North Carolina Division of Public Health
Immunization Branch
1917 Mail Service Center
Raleigh, NC 27699-1917
Fed Ex: 5601 Six Forks Road
2nd Floor
Raleigh, NC 27609-3811

PHONE #: (919) 707-5550
FAX #: (919) 870-4824
Program Manager: Beth Rowe-West
Email: beth.rowe-west@ncmail.net

NORTH DAKOTA
North Dakota Department of Health
Division of Disease Control
State Capitol
600 East Boulevard
Bismarck, North Dakota 58505-0200

PHONE #: (701) 328-2378
FAX #: (701) 328-1412
Program Manager: Molly Sander
Email: msander@nd.gov

OHIO
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Licensure of a Haemophilus influenzae Type b (Hib) Vaccine (Hiberix) and Updated Recommendations for Use of Hib Vaccine

On August 19, 2009, the Food and Drug Administration (FDA) licensed Hiberix (GlaxoSmithKline Biologicals, Rixensart, Belgium), a *Haemophilus influenzae* type b (Hib) conjugate vaccine composed of *H. influenzae* type b capsular polysaccharide (polyribosyl-ribitol-phosphate [PRP]) conjugated to inactivated tetanus toxoid (PRP-T). Hiberix is licensed for use as the booster (final) dose of the Hib vaccine series for children aged 15 months through 4 years (before the 5th birthday) who have received previously the primary series of Hib vaccination (consisting of 2 or 3 doses, depending on the formulation) (*1*). The Advisory Committee on Immunization Practices (ACIP) recommends Hib booster vaccination for children at ages 12 through 15 months; however, because of the recent shortage of Hib vaccines, many children have deferred the booster dose and therefore require catch-up vaccination (*2*). This report summarizes the indications for Hiberix use and provides guidance on Hib booster dose administration based on increasing vaccine supplies. Vaccination recommendations in this report update the previous advisory on Hib booster administration (June 26, 2009) (*2*), which advised that children with deferred booster doses receive it at the next regularly scheduled visit. Vaccination providers are now recommended to begin recall of children in need of the booster dose when feasible and monovalent Hib vaccine supply in the office is adequate.

Hiberix Licensure

FDA licensed the new vaccine after review of safety and immunogenicity data from seven core studies conducted outside the United States that evaluated Hiberix for the booster dose in 1,008 children (*3,4*). The children in these studies received various Hib conjugate vaccines for the primary series, including Hiberix (not approved for primary series in the United States), and the monovalent Hib vaccines currently licensed for primary series in the United States, ActHIB (PRP-T, Sanofi Pasteur, Swiftwater, Pennsylvania) and PedvaxHIB (PRP-OMP, Merck & Co., Inc., West Point, Pennsylvania). In the seven core studies, Hiberix was given concomitantly with one of the following vaccines (all non-U.S. formulations, not licensed in the United States; GlaxoSmithKline Biologicals): diphtheria, tetanus, and acellular pertussis vaccine (DTaP), DTaP-hepatitis B vaccine (DTaP-HBV), DTaP-HBV-inactivated polio vaccine (DTaP-HBV-IPV), or DTaP-inactivated polio vaccine (DTaP-IPV). Serologic endpoints showed that the booster dose of Hiberix provided levels of antibodies protective against Hib invasive disease. Rates of adverse events generally were comparable to those observed with other childhood vaccines. In one of the core studies with 371 children, the frequencies of solicited local symptoms (i.e., redness, pain, or swelling) were each less than 25% (*3*), comparable to that reported in studies of currently licensed monovalent Hib conjugate vaccines (*1*). Hiberix was first introduced to markets outside the United States in 1996 and is used in nearly 100 countries (*3,4*).

Hiberix is supplied as a lyophilized powder for reconstitution in sterile 0.9% saline solution (*3*). Each 0.5 mL intramuscular dose of Hiberix contains 10 μg of purified *H. influenzae* type b capsular polysaccharide (polyribosyl-ribitol-phosphate [PRP]) conjugated to inactivated tetanus toxoid (PRP-T) (*3*). Hiberix does not contain thimerosal (*3*).

Indications and Guidance for Use

Hiberix is licensed for use as the booster (final) dose for Hib vaccination for children aged 15 months through 4 years (before the 5th birthday) who have received a primary Hib vaccination series of 2 or 3 doses (depending on the formulation of the primary series vaccines). ACIP recommends Hib booster dosing at ages 12 through 15 months (*1*). To facilitate timely booster vaccination, Hiberix and other Hib conjugate vaccines can be administered as early as age 12 months, in accordance with Hib vaccination schedules for routine and catch-up immunization (*5*). Hiberix is not licensed for the primary Hib vaccination series; however, if Hiberix is administered inadvertently during the primary vaccination series, the dose should be counted as a valid PRP-T dose that does not need to be repeated if it was administered according to schedule (*5*). In these children, a total of 3 doses will complete the routine primary series.

Children aged 12 months through 4 years (before the fifth birthday) who did not receive a booster because of the recent shortage of Hib vaccines should receive a booster with any of the available Hib-containing vaccines at the earliest opportunity (*2*). With licensure of Hiberix and anticipated distribution, the increased supply of Hib-containing vaccines will be sufficient to support a provider-initiated notification process to contact all children whose Hib booster dose had been deferred. When feasible and when vaccine supply in the office is sufficient, vaccination providers should review electronic or paper medical records or immunization information system (e.g., registry) records to identify and recall children in need of a booster dose. If supplies are not adequate, providers should continue to follow previous recommendations to provide the booster dose at the child's next regularly scheduled visit (*2*).

Information Regarding Supply of Hiberix, ActHib, and Pentacel

At this time, production of Merck Hib vaccine products remains suspended; however, supplies of Sanofi Pasteur vaccines ActHIB (monovalent Hib vaccine) and Pentacel (DTaP-IPV/Hib) are available for use for the primary Hib vaccination series and booster in infants and children. Vaccination providers with questions about supplies of Hiberix monovalent Hib vaccine purchased with nonpublic funds should contact GlaxoSmithKline Biologicals' customer service department (telephone, 866-475-8222). Providers with questions about supplies of ActHIB or Pentacel purchased with nonpublic funds should contact Sanofi Pasteur's customer service department (telephone, 800-822-2463). For public vaccine supplies, including Vaccines for Children Program vaccine, providers should contact their state/local immunization program to obtain vaccine. Providers ordering Hiberix through the Vaccines for Children Program may place orders in early October.

This recommendation reflects CDC's assessment of the existing national Hib vaccine supply and will be updated if the supply changes. Updated information about the national Hib vaccine supply is available at http://www.cdc.gov/vaccines/vac-gen/shortages/default.htm. Details about the routine Hib vaccination schedule are available at http://www.cdc.gov/vaccines/recs/schedules/default.htm#child. Adverse events after receipt of any vaccine should be reported to the Vaccine Adverse Event Reporting System at http://vaers.hhs.gov.

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Updated Recommendations from the Advisory Committee on Immunization Practices (ACIP) for Use of Hepatitis A Vaccine in Close Contacts of Newly Arriving International Adoptees

On February 25, 2009, the Advisory Committee on Immunization Practices (ACIP) recommended routine hepatitis A vaccination for household members and other close personal contacts (e.g., regular babysitters) of adopted children newly arriving from countries with high or intermediate hepatitis A endemicity. This new recommendation complements previous ACIP recommendations for hepatitis A vaccination for persons traveling from the United States to countries with high or intermediate hepatitis A endemicity (*1*,*2*) (including persons with travel related to international adoption), and postexposure prophylaxis for contacts of persons with hepatitis A (*1*). This report introduces the new recommendation and outlines the underlying epidemiologic and programmatic rationale.

Rationale and Methods

Hepatitis A virus (HAV) can produce either asymptomatic or symptomatic infection in humans after an average incubation period of 28 days (range: 15--50 days) (*3*). Peak infectivity occurs during the 2-week period before onset of jaundice or elevation of liver enzymes, when concentration of virus in stool is highest (*4*). Illness caused by HAV typically has an abrupt onset that can include fever, malaise, anorexia, nausea, abdominal discomfort, dark urine, and jaundice. The likelihood of having symptoms with HAV infection increases with age. Fewer than 10% of infections among children aged 0--4 years result in jaundice; this percentage increases to 30%--40% among children aged 5--9 years, 60%--80% among youths aged 10--17 years, and 80%--90% among adults aged ≥18 years (*5*). When signs and symptoms occur, typically they last <2 months, although 10%--15% of symptomatic persons have prolonged or relapsing disease lasting up to 6 months (*6*). The case-fatality rate for HAV infection increases with age: 1.8% for persons adults aged >50 years compared with 0.6% for persons aged <50 years. The case-fatality rate is also increased among persons with chronic liver disease, who are at increased risk for acute liver failure (*7*).

In making its recommendation, ACIP considered the likelihood that a child adopted by parents in the United States might be actively infected with HAV and shedding virus at the time of adoption. During 1998--2008, approximately 18,000 children (range: 15,583 to 22,884) were adopted from foreign countries by families in the United States each year.* Approximately 99.8% of these children came from countries where hepatitis A is considered to be of high or intermediate endemicity (*2*), and approximately 85% of were aged <5 years. Country-specific policies pertaining to foreign adoption are changing constantly, leading to rapid changes in the numbers of international adoptees entering the United States from various countries. Although South Korea was the most common country of origin for adoptions in the United States in the early 1990s, Russia and China became prominent in international adoption in the late 1990s, and currently the largest numbers of adopted children come from Guatemala, China, Russia, and Ethiopia. The incidence of HAV infection is highest in these countries among children aged <5 years, when HAV infection

is likely to be asymptomatic.

ACIP also considered recent reports of HAV infection among persons in close contact with new adoptees from countries of high or intermediate hepatitis A endemicity. Such persons are at greater risk for HAV infection. In 2007, CDC was notified of a case of fulminant hepatitis A in a nontraveling household contact of an asymptomatic Ethiopian adoptee confirmed to have acute hepatitis A (immunoglobulin M [IgM] antibody to HAV [anti-HAV] positive). This case prompted further investigation that led to identification of 20 other cases of acute hepatitis A among persons who had close personal contact with newly arriving internationally adopted children and no history of traveling abroad (*8*). Two acute hepatitis A cases were identified among traveling parents who had not been vaccinated. This same study found that 98% of parents traveling to pick up their children had been vaccinated against hepatitis A in accordance with existing ACIP recommendations (*8*).

Since 2007, CDC has received 14 additional reports of acute hepatitis A following exposure to nonjaundiced adoptees newly arriving from countries of high or intermediate hepatitis A endemicity. Although these numbers are small compared with the total number of hepatitis A cases (2,979) reported to CDC in 2007 (*9*), they likely represent an underestimate of the number of hepatitis A cases associated with international adoptions because contact with an international adoptee is not asked routinely as part of national hepatitis A surveillance. All of the 14 adoptee-associated cases identified since 2007 were in close contacts who had not been vaccinated against hepatitis A and had no history of travel and no other risk factors for hepatitis A. In one instance, both adoptive parents developed hepatitis A that required hospitalization (CDC, unpublished data, 2008). In another instance, a 2008 community outbreak with 12 hepatitis A cases was associated with an asymptomatic HAV-infected international adoptee; two infected contacts were hospitalized, and disease was identified among tertiary contacts in an elementary school (CDC, unpublished data, 2009).

Data from a study conducted at three adoption clinics in the United States, each screening 100--200 incoming adoptees for hepatitis A each year, indicate that 1%--6% of newly arrived international adoptees are acutely infected with HAV (non-jaundiced; IgM anti-HAV positive). A proportion of these adoptees represent a source of infection for susceptible close contacts (*9*). The risk for hepatitis A among close personal contacts of international adoptees is estimated at 106 (range: 90--819) per 100,000 household contacts of international adoptees within the first 60 days of their arrival in the United States (CDC, unpublished data, 2009). By comparison, according to surveillance data, the estimated rate of symptomatic hepatitis A in the U.S. general population in 2007 was 1.0 per 100,000 population (*10*).

Updated Recommendation

Based on this evidence, on February 25, ACIP updated its guidance by recommending hepatitis A vaccination for all previously unvaccinated persons who anticipate close personal contact (e.g., household contact or regular babysitting) with an international adoptee from a country of high or intermediate endemicity during the first 60 days following arrival of the adoptee in the United States. The first dose of the 2-dose hepatitis A vaccine series should be administered as soon as adoption is planned, ideally 2 or more weeks before the arrival of the adoptee.

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* Additional information available at http://adoption.state.gov/news/total_chart.html.

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FDA Licensure of Bivalent Human Papillomavirus Vaccine (HPV2, Cervarix) for Use in Females and Updated HPV Vaccination Recommendations from the Advisory Committee on Immunization Practices (ACIP)

Weekly

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Please note: An erratum has been published for this article. To view the erratum, please click here.

On October 16, 2009, the Food and Drug Administration (FDA) licensed bivalent human papillomavirus vaccine (HPV2; Cervarix, GlaxoSmithKline) for use in females aged 10 through 25 years. Cervarix is the second human papillomavirus (HPV) vaccine licensed for use in females in the United States. Quadrivalent HPV vaccine (HPV4; Gardasil, Merck & Co, Inc.) was licensed in 2006 for use in females aged 9 through 26 years, and the Advisory Committee on Immunization Practices (ACIP) recommended routine HPV4 vaccination of females aged 11 or 12 years, and catch-up vaccination for females aged 13 through 26 years

(*1*). This report provides updated recommendations for routine and catch-up vaccination of females with either HPV2 or HPV4.

Both HPV2 and HPV4 are composed of virus-like particles (VLPs) prepared from recombinant L1 capsid protein of HPV; the two vaccines are not live vaccines (Table 1). HPV2 is directed against two oncogenic types (HPV 16 and 18). HPV4 is directed against two oncogenic types (HPV 16 and 18) and two nononcogenic types (HPV 6 and 11). Both vaccines have high efficacy against HPV 16 and 18-related cervical precancer lesions. HPV4 also has high efficacy against HPV 6 and HPV 11-related genital warts and HPV 16 and 18-related vaginal and vulvar precancer lesions (Table 2) (*2*--*5*).

HPV 16 and 18 cause about 70% of cervical cancers; each of the other oncogenic HPV types accounts for a small percentage of all cervical cancers. Other HPV-associated cancers in females include a subset of vulvar, vaginal, anal, and oropharyngeal and oral cavity cancers, caused primarily by HPV 16. HPV 6 and 11 cause approximately 90% of genital warts and most cases of recurrent respiratory papillomatosis.

In anticipation of FDA licensure of HPV2, ACIP reviewed data on the immunogenicity, efficacy, and safety of HPV2, as well as information on HPV4. At its October 21, 2009, meeting, ACIP approved updated recommendations for use of HPV vaccines in females.

HPV2 Clinical Trial Data

HPV2 efficacy was evaluated in two randomized, double-blind, controlled clinical trials in females aged 15 through 25 years, including a phase IIb study (*6,7*) and a phase III study (*4*). The phase III trial included 18,644 females, followed for a mean of 34.9 months. Efficacy against HPV 16 or 18-related cervical intraepithelial neoplasia grade 2 or 3 or adenocarcinoma in situ (CIN2+) was 92.9% in the according to protocol analysis (Table 2) (*4*). Among women who were HPV 16 or 18 DNA positive at study enrollment, the vaccine had no efficacy against CIN2+ due to that type. A subset of participants in the phase IIb study has been followed for up to 6.4 years (mean: 5.9 years) after dose one with high efficacy against HPV 16 or 18-related CIN2+ demonstrated throughout the follow-up period (*7*).

Protection against cervical lesions due to nonvaccine HPV types was evaluated. In an analysis limited to lesions without HPV 16 or 18 coinfection, efficacy against CIN2+ due to any of 12 nonvaccine oncogenic types (HPV 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) was 37.4% (96.1% confidence interval [CI] = 7.4--58.2). In a post hoc analysis, efficacy against HPV 31-related CIN2+ in the according to protocol population was 89.4% (99.7% CI = 29.0--99.7) (*5*).

In all studies, ≥99% of participants developed an HPV 16 and 18 antibody response 1 month after completing the 3-dose series. Bridging immunogenicity studies were conducted among 1,193 females aged 10 through 14 years; geometric mean titers (GMTs) 1 month after the third dose were noninferior to those in females aged 15 through 25 years (*5*). The antibody responses for all vaccine antigens were noninferior after concomitant administration of HPV2 with tetanus toxoid, diphtheria toxoid, and acellular pertussis vaccine and/or with meningococcal conjugate vaccine in females aged 11 through 18 years compared with those after administration at separate visits. Rates of solicited and unsolicited symptoms and events were similar in all study groups (*8*).

HPV2 vaccinees were evaluated for injection-site and systemic symptoms, medically significant conditions, new onset autoimmune disorders, new onset chronic diseases, deaths, serious adverse events, and pregnancy outcomes. Safety was evaluated by pooling data from 11 clinical trials of bivalent vaccine in females aged 10 through 25 years (*9*), and by a meta-analysis of safety databases of bivalent vaccine as well as other vaccines with the same adjuvant (*10*). The pooled safety analysis included 23,713 females aged 10 through 25 years; approximately 12,000 females received at least 1 dose of HPV2. In an analysis of local and general adverse events, a larger proportion of persons reported at least one injection-site symptom in the HPV2 group compared with controls (*5*). In the HPV2 group, 92% reported injection-site pain, 48% redness, and 44% swelling compared with 64%--87%, 24%--28%, and 17%--21% in the control groups. Fatigue, headache, and myalgia were the most common general symptoms. No differences were observed in unsolicited symptoms within 30 days of vaccination between the vaccine group and control groups.

Serious adverse events and deaths were evaluated in a pooled safety analysis that included 29,953 females aged 10 through 72 years (16,142 received HPV2). Proportions of persons reporting a serious adverse event were similar in vaccine and control groups (5.3% and 5.9%, respectively), as were the types of serious adverse events reported (*5*). In the pooled safety analysis, including 12,533 women who received HPV2 and over 10,730 in the control groups, incidence of potential new autoimmune disorders did not differ (0.8% in both groups).

Clinical protocols excluded women who were pregnant, and participants were instructed to avoid pregnancy until 2 months after the last vaccination. However, 3,696 pregnancies occurred in the vaccine group and 3,580 in the pooled control groups. Overall, no differences were observed in rates of any specific pregnancy outcomes between groups (*5*). Among 761 pregnancies around the time of vaccination (defined as last menstrual period 30 days before to 45 days after vaccination), 13.6% of pregnancies ended in spontaneous abortion in the vaccine group compared with 9.6% in the control group. HPV2 has been classified as Category B on the basis of animal studies that revealed no evidence of impaired fertility or harm to the fetus. No data are available on use of HPV2 in lactating women.

Vaccine Recommendations for HPV2 and HPV4

ACIP recommends routine vaccination of females aged 11 or 12 years with 3 doses of either HPV2 or HPV4. The vaccination series can be started beginning at age 9 years.

Vaccination is recommended for females aged 13 through 26 years who have not been vaccinated previously or who have not completed the 3-dose series. If a female reaches age 26 years before the vaccination series is complete, remaining doses can be administered after age 26 years. Ideally, vaccine should be administered before potential exposure to HPV through sexual contact.

ACIP recommends vaccination with HPV2 or HPV4 for prevention of cervical cancers and precancers. Both vaccines might provide protection against some other HPV-related cancers in addition to cervical cancer, although there are currently only data sufficient to recommend HPV4 for protection against vulvar and vaginal cancers and precancers. HPV4 is recommended also for prevention of genital warts.

Dosage, Administration, and Schedules

The dosing and administration schedules are the same for HPV4 and HPV2. Each dose is 0.5 mL, administered intramuscularly, preferably in a deltoid muscle. The vaccines are administered in a 3-dose schedule. The second dose is administered 1 to 2 months after the first dose, and the third dose is administered 6 months after the first dose.

The minimum interval between the first and second dose of vaccine is 4 weeks and between the second and third dose is 12 weeks. The minimum interval between the first and third dose is 24 weeks. Doses received after a shorter-than-recommended dosing interval should be readministered. If the HPV vaccine schedule is interrupted, the vaccine series does not need to be restarted. Coadministration of a different inactivated or live vaccine, either simultaneously or at any time before or after HPV vaccine, is permitted because neither HPV vaccine is a live vaccine.

Whenever feasible, the same HPV vaccine should be used for the entire vaccination series. No studies address interchangeability of HPV vaccines. However, if the vaccine provider does not know or have available the HPV vaccine product previously administered, either HPV vaccine can be used to complete the series to provide protection against HPV 16 and 18. For protection against HPV 6 or 11-related genital warts, a vaccination series with less than 3 doses of HPV4 might provide less protection against genital warts than a complete 3-dose HPV4 series.

Special Situations

Females who have abnormalities on their cervical cancer screening results are likely to be infected with one or more genital HPV types. With increasing severity of Papanicolau (Pap) findings, the likelihood of infection with HPV 16 or 18 increases, and benefits of vaccination decrease. Vaccination is still recommended for

such females, because vaccination can provide protection against infection with HPV vaccine types not already acquired. Females should be advised that vaccination will have no therapeutic effect on an existing HPV infection or abnormal Pap test.

Prevaccination assessments (e.g., Pap testing or screening for high-risk HPV DNA, type-specific HPV tests, or HPV antibody) to establish the appropriateness of HPV vaccination are not recommended at any age.

A history of genital warts or clinically evident genital warts indicates infection with HPV, most often HPV 6 or 11. Vaccination is still recommended for such females because vaccination can provide protection against infection with HPV vaccine types not already acquired. Females should be advised that vaccination will have no therapeutic effect on an existing HPV infection or genital warts.

Lactating women can receive HPV vaccine.

HPV2 and HPV4 are not live vaccines, and can be administered to females who are immunosuppressed (from disease or medications). However, the immune response and vaccine efficacy might be less than that in immunocompetent persons.

Precautions and Contraindications

HPV vaccines are not recommended for use in pregnant women. If a woman is found to be pregnant after initiating the vaccination series, the remainder of the 3-dose series should be delayed until completion of pregnancy. Pregnancy testing is not needed before vaccination. If a vaccine dose has been administered during pregnancy, no intervention is needed.

Patients and health-care providers should report any exposure to HPV4 during pregnancy to Merck at telephone, 800-986-8999, and any exposure to HPV2 during pregnancy to GlaxoSmithKline at telephone, 888-452-9622.

HPV vaccines can be administered to persons with minor acute illnesses. Vaccination of persons with moderate or severe acute illnesses should be deferred until after the patient improves.

Syncope can occur after vaccination and has been observed among adolescents and young adults. To avoid serious injury related to a syncopal episode, vaccine providers should consider observing patients for 15 minutes after they are vaccinated.

HPV vaccines are contraindicated for persons with a history of immediate hypersensitivity to any vaccine component. HPV4 is produced in *Saccharomyces cerevisiae* (baker's yeast) and is contraindicated for persons with a history of immediate hypersensitivity to yeast. Prefilled syringes of HPV2 have latex in the rubber stopper and should not be used in persons with anaphylactic latex allergy. HPV2 single dose vials contain no latex.

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TABLE 1. Selected characteristics of quadrivalent human papillomavirus vaccine (HPV4) and bivalent human papillomavirus vaccine (HPV2)*

Characteristic	HPV4	HPV2
Manufacturer	Merck & Co, Inc.	GlaxoSmithKline
Vaccine composition (L1 protein)	20 μg HPV 6 40 μg HPV 11 40 μg HPV 16 20 μg HPV 18	20 μg HPV 16 20 μg HPV 18
Manufacturing	Saccharomyces cerevisiae (bread yeast), expressing L1	Trichoplusia ni insect cell line infected with L1 encoding recombinant baculovirus
Adjuvant	AAHS: 225 μg amorphous aluminum	AS04: 500 μg aluminum hydroxide

	hydroxyphosphate sulfate	50 μg 3-O-desacyl-4' monophosphoryl lipid A
Preservatives	None	None
Other content	Sodium chloride, L-histidine, polysorbate 80, sodium borate, and water for injection	Sodium chloride and sodium dihydrogen phosphate dehydrate, and water for injection
Temperature storage	Store refrigerated at 36°--46°F (2°--8°C).	Store refrigerated at 36°--46°F (2°--8°C).
	Do not freeze.	Do not freeze.
Volume per dose	0.5 mL	0.5 mL
Administration	Intramuscular	Intramuscular
	3 doses	3 doses
Schedule/Intervals	Second and third doses 1 to 2 months and 6 months after first dose	Second and third doses 1 to 2 months and 6 months after first dose

* Both vaccines are composed of virus-like particles (VLPs) prepared from recombinant L1 capsid protein of human papillomavirus (HPV); the vaccines are not live vaccines.

TABLE 2. Efficacy of bivalent human papillomavirus vaccine (HPV2) and quadrivalent human papillomavirus vaccine (HPV4) in females

Vaccine/Endpoint/HPV type	Vaccine		Control		Vaccine efficacy	
	No.	Cases	No.	Cases	%	(CI*)
Bivalent vaccine (HPV2)†						(96.1% CI)
CIN2/3 or AIS§						
HPV 16 and/or 18	7,344	4	7,312	56	92.9	(79.9--98.3)

HPV 16	6,303	2	6,165	46	95.7	(82.9--99.6)
HPV 18	6,794	2	6,746	15	86.7	(39.7--98.7)
Quadrivalent vaccine (HPV4)¶						(95% CI)
CIN2/3 or AIS**						
HPV 6, 11, 16, and/or 18	7,864	2	7,865	110	98.2	(93.3--99.8)
HPV 16	6,647	2	6,455	81	97.6	(91.1--99.7)
HPV 18	7,382	0	7,316	29	100.0	(86.6--100.0)
VIN2/3 or VaIN2/3 **						
HPV 6, 11, 16, and/or 18	7,900	0	7,902	23	100.0	(82.6--100.0)
HPV 16	6,654	0	6,467	17	100.0	(76.5--100.0)
HPV 18	7,414	0	7,343	2	100.0	(<0--100.0)
Genital warts††						
HPV 6 and/or 11	6,932	2	6,856	189	99.0	(96.2--99.9)

Abbreviations: CIN2/3 = cervical intraepithelial neoplasia grade 2 or 3, AIS = adenocarcinoma in situ, VIN2/3 = vulvar intraepithelial neoplasia grade 2 or 3, VaIN2/3 = vaginal intraepithelial neoplasia grade 2 or 3, HPV = human papillomavirus.

* Confidence interval.

† Phase III trial. According to protocol efficacy analysis included females aged 15 through 25 years who received all 3 vaccine doses, were seronegative at day 1 and HPV DNA negative at day 1 through month 6 for the respective HPV type, and had normal or low grade cytology at day 1, with case counting beginning 1 day after third vaccine dose; mean duration of follow-up post first vaccine dose: 34.9 months.

§ **Source:** Paavonen J, Naud P, Salmeron J, et al. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. Lancet 2009;374:301--14.

¶ Combined analysis of one phase II and two phase III trials. Per protocol efficacy analysis included

females aged 16 through 26 years who received all 3 vaccine doses, were seronegative at day 1 and HPV DNA negative at day 1 through month 7 for the respective HPV type, with case counting beginning 1 month after third vaccine dose; mean duration of follow-up post first vaccine dose: 42 months.

** Source: Kjaer SK, Sigurdsson K, Iversen OE, et al. A pooled analysis of continued prophylactic efficacy of quadrivalent human papillomavirus (Types 6/11/16/18) vaccine against high-grade cervical and external genital lesions. Cancer Prev Res 2009;2:868--78.

†† Source: Food and Drug Administration. Product approval-prescribing information [package insert]. Gardasil [human papillomavirus quadrivalent (types 6, 11, 16, and 18) vaccine, recombinant], Merck & Co, Inc: Food and Drug Administration 2009. Available at http://www.fda.gov/biologicsbloodvaccines/vaccines/approvedproducts/ucm094042.htm. Accessed May 25, 2010.

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FDA Licensure of Quadrivalent Human Papillomavirus Vaccine (HPV4, Gardasil) for Use in Males and Guidance from the Advisory Committee on Immunization Practices (ACIP)

Weekly

May 28, 2010 / 59(20);630-632

On October 16, 2009, the Food and Drug Administration licensed quadrivalent human papillomavirus vaccine (HPV4; Gardasil, Merck & Co. Inc.) for use in males aged 9 through 26 years for prevention of genital warts caused by human papillomavirus (HPV) types 6 and 11. HPV4 had been licensed previously for use in females aged 9 through 26 years for prevention of HPV 6, 11, 16, and 18-related outcomes (i.e., vaginal, vulvar, and cervical precancers and cancers and genital warts). The Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination of females at age 11 or 12 years and catch-up vaccination for females aged 13 through 26 years (*1*). On October 21, 2009, ACIP provided guidance that HPV4 may be given to males aged 9 through 26 years to reduce their likelihood of acquiring genital warts; ACIP does not recommend HPV4 for routine use among males. This report presents the ACIP policy

statement and summarizes background data. Issues reviewed by ACIP included efficacy, immunogenicity, and safety of the HPV4 vaccine in males, epidemiology of HPV and burden of HPV-associated diseases and cancers in males, cost-effectiveness of male vaccination, and programmatic considerations.

HPV types 6 and 11 cause approximately 90% of genital warts and most cases of recurrent respiratory papillomatosis. Approximately 500,000 cases of genital warts are estimated to occur each year in the United States among sexually active men and women (*2,3*). Direct medical costs related to genital warts are estimated at $200 million per year (*2,3*)*;* in addition, genital warts can have an adverse impact on quality of life (*4*). HPV-associated cancers in males include certain anal, penile, and oropharyngeal and oral cavity cancers caused primarily by HPV 16.

HPV4 has high efficacy for prevention of genital warts. The phase III efficacy study enrolled 4,065 males aged 16 through 26 years. Participants were enrolled from North America, South America, Europe, Australia, and Asia. The efficacy for prevention of genital warts related to HPV types 6, 11, 16, or 18 among males who received all 3 vaccine doses and were seronegative at day 1, and DNA negative day 1 through month 7 to the respective HPV type (per protocol population) was 89.4%; the efficacy for HPV 6 or 11-related genital warts alone was approximately the same (Table) (*5*). The efficacy for prevention of HPV 6, 11, 16, or 18-related genital warts among males who received at least 1 vaccine dose and regardless of baseline DNA or serology (intent to treat population), was 67.2%, and the efficacy for prevention of genital warts related to any HPV type was 62.1% (Table) (*5*). No evidence of efficacy was observed among males who were infected with the respective HPV type at baseline. The median duration of follow-up at the time of the study's interim analysis was approximately 2.3 years.

Data on immunogenicity in males are available from the phase III trial conducted among males aged 16 through 26 years, and from bridging immunogenicity studies conducted among males aged 9 through 15 years (*5*). Seroconversion rates were high for all four HPV types (HPV 6, 11, 16, or 18) targeted by HPV4, and postvaccination antibody titers were significantly higher in males aged 9 through 15 years compared with males aged 16 through 26 years (*5*).

As observed previously with females, in the clinical trials for males, the most common adverse events were injection-site reactions, most of which were mild or moderate in intensity (*5*). Headache and fever were the most commonly reported systemic adverse reactions in both treatment groups (*5*). Postlicensure data in females indicate that HPV4 adverse events are similar to adverse events reported following administration of other vaccines to adolescents (*6*).

Mathematical modeling suggests that adding male HPV vaccination to a female-only HPV vaccination program is not the most cost-effective vaccination strategy for reducing the overall burden of HPV-associated conditions in males and females when vaccination coverage of females is high (>80%) (*7*). When coverage of females is less than 80%, male vaccination might be cost-effective, although results vary substantially across models (*7*). Because the health burden is greater in females than males, and numerous models have shown vaccination of adolescent girls to be a cost-effective use of public health resources, improving coverage in females aged 11 and 12 years could potentially be a more effective and cost-effective strategy than adding male vaccination.

Men who have sex with men (MSM) are particularly at risk for conditions associated with HPV types 6, 11, 16, and 18; diseases and cancers that have a higher incidence among MSM include anal intraepithelial neoplasias, anal cancers, and genital warts (*8,9*). HPV4 has high efficacy for prevention of anal intraepithelial neoplasias in MSM (*10*); however, this information was not available before the October 2009 ACIP meeting and has not yet been reviewed by FDA.

Vaccine Guidance

The 3-dose series of HPV4 may be given to males aged 9 through 26 years to reduce their likelihood of acquiring genital warts. HPV4 would be most effective when given before exposure to HPV through sexual contact.

Administration, Special Situations, Precautions, and Contraindications

HPV4 is administered in a 3-dose schedule. The second dose is administered 1 to 2 months after the first dose, and the third dose is administered 6 months after the first dose. The minimum interval between the first and second dose of vaccine is 4 weeks, and the minimum interval between the second and third dose is 12 weeks. The minimum interval between the first and third dose is 24 weeks. Doses received after a dosing interval that is shorter than recommended should be readministered.

If the HPV vaccine schedule is interrupted, the vaccine series does not need to be restarted. Coadministration of a different inactivated or live vaccine, either simultaneously or at any time before or after HPV4 is permitted because HPV4 is not a live vaccine.

HPV4 can be administered to persons who are immunosuppressed (from disease or medications). However, the immune response and vaccine efficacy might be less than that in immunocompetent persons.

HPV4 can be administered to persons with minor acute illnesses. Vaccination of persons with moderate or severe acute illnesses should be deferred until after the patient improves.

Syncope can occur after vaccination and has been observed among adolescents and young adults. To avoid serious injury related to a syncopal episode, vaccine providers should consider observing patients for 15 minutes after they are vaccinated.

HPV4 is contraindicated for persons with a history of immediate hypersensitivity to any vaccine component. HPV4 is a recombinant vaccine produced in *Saccharomyces cerevisiae* (baker's yeast) and is contraindicated for persons with a history of immediate hypersensitivity to yeast.

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TABLE. Efficacy of quadrivalent human papillomavirus vaccine (HPV4) for prevention of genital warts in males aged 16 through 26 years

	Vaccine		Control		Vaccine efficacy	
Endpoint	**No.**	**Cases**	**No.**	**Cases**	**%**	**(95% CI*)**
Per protocol efficacy†,§						
HPV 6, 11, 16, and/or 18-related	1,397	3	1,408	28	89.4	(65.5--97.9)
Intent to treat efficacy¶						
HPV 6, 11, 16, and/or 18-related	1,943	24	1,937	72	67.2	(47.3--80.3)
Any type-related	1,943	32	1,937	83	62.1	(42.4--75.6)

Source: Food and Drug Administration. Product approval-prescribing information [package insert]. Gardasil [human papillomavirus quadrivalent (types 6, 11, 16, and 18) vaccine, recombinant], Merck & Co, Inc: Food and Drug Administration 2009. Available at http://www.fda.gov/biologicsbloodvaccines/vaccines/approvedproducts/ucm094042.htm. Accessed May 25, 2010.

* Confidence interval.

† Population included males who received all 3 vaccine doses, were seronegative at day 1, and DNA negative at day 1 through month 7 to the respective human papillomavirus (HPV) type, with case counting beginning after month 7.

§ Efficacy for genital warts (HPV 6 and/or 11-related) was 89% (95% CI = 66--98). **Source:** Food and Drug Administration. Vaccine and Related Biological Products Advisory Committee meeting presentations. September 9, 2009. Available at http://www.fda.gov/advisorycommittees/committeesmeetingmaterials/bloodvaccinesandotherbiologics/vaccinesandrelatedbiologicalproductsadvisorycommittee/ucm183835.htm.

¶ Population included all males who received at least 1 vaccine dose, regardless of baseline DNA or serology, with case counting beginning after day 1.

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Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010



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Prevention and Control of Influenza with Vaccines

Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010

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Summary

This report updates the 2009 recommendations by CDC's Advisory Committee on Immunization Practices (ACIP) regarding the use of influenza vaccine for the prevention and control of influenza (CDC. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices [ACIP]. MMWR 2009;58[No. RR-8] and CDC. Use of influenza A (H1N1) 2009 monovalent vaccine—recommendations of the Advisory Committee on Immunization Practices [ACIP], 2009. MMWR 2009;58:[No. RR-10]). The 2010 influenza recommendations include new and updated information. Highlights of the 2010 recommendations include 1) a recommendation that annual vaccination be administered to all persons aged ≥6 months for the 2010–11 influenza season; 2) a recommendation that children aged 6 months–8 years whose vaccination status is unknown or who have never received seasonal influenza vaccine before (or who received seasonal vaccine for the first time in 2009–10 but received only 1 dose in their first year of vaccination) as well as children who did not receive at least 1 dose of an influenza A (H1N1) 2009 monovalent vaccine regardless of previous influenza vaccine history should receive 2 doses of a 2010–11 seasonal influenza vaccine (minimum interval: 4 weeks) during the 2010–11 season; 3) a recommendation that vaccines containing the 2010–11 trivalent vaccine virus strains A/California/7/2009 (H1N1)-like (the same strain as was used for 2009 H1N1 monovalent vaccines), A/Perth/16/2009 (H3N2)-like, and B/Brisbane/60/2008-like antigens be used; 4) information about Fluzone High-Dose, a newly approved vaccine for persons aged ≥65 years; and 5) information about other standard-dose newly approved influenza vaccines and previously approved vaccines with expanded age indications. Vaccination efforts should begin as soon as the 2010–11 seasonal influenza vaccine is available and continue through the influenza season. These recommendations also include a summary of safety data for U.S.-licensed influenza vaccines. These recommendations and other information are available at CDC's influenza website (http://www.cdc.gov/flu); any updates or supplements that might be required during the 2010–11 influenza season also will be available at this website. Recommendations for influenza diagnosis and antiviral use will be published before the start of the 2010–11 influenza season. Vaccination and health-care providers should be alert to announcements of recommendation updates and should check the CDC influenza website periodically for additional information.

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Introduction

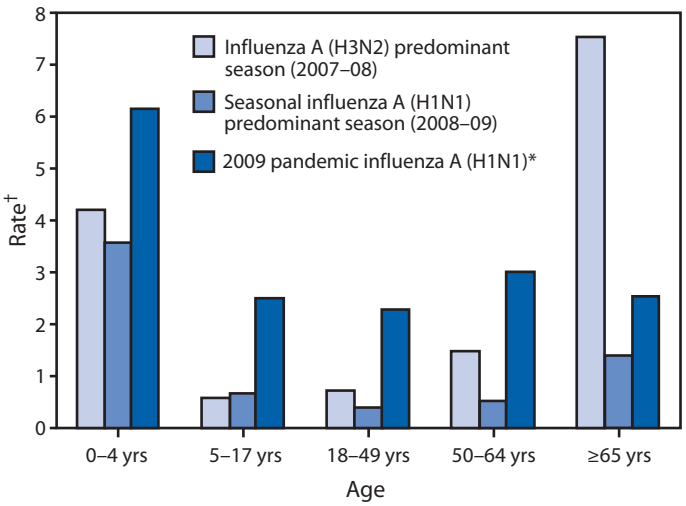
In the United States, annual epidemics of influenza occur typically during the late fall through early spring. Influenza viruses can cause disease among persons in any age group, but rates of infection are highest among children (*1–3*). During these annual epidemics, rates of serious illness and death are highest among persons aged ≥65 years, children aged <2 years, and persons of any age who have medical conditions that

place them at increased risk for complications from influenza (*1,4,5*). Influenza epidemics were associated with estimated annual averages of approximately 36,000 deaths during 1990–1999 and approximately 226,000 hospitalizations during 1979–2001 (*6,7*).

Influenza A subtypes that are generated by a major genetic reassortment (i.e., antigenic shift) or that are substantially different from viruses that have caused infections over the previous several decades have the potential to cause a pandemic (*8*). In April 2009, a novel influenza A (H1N1) virus, 2009 influenza A (H1N1), that is similar to but genetically and antigenically distinct from influenza A (H1N1) viruses previously identified in swine, was determined to be the cause of respiratory illnesses that spread across North America and were identified in many areas of the world by May 2009 (*9,10*). Influenza morbidity caused by 2009 pandemic influenza A (H1N1) remained above seasonal baselines throughout spring and summer 2009 and was the cause of the first pandemic since 1968. In the United States, the pandemic was characterized by a substantial increase in influenza activity, as measured by multiple influenza surveillance systems, that was well beyond historical norms in September 2009, peaking in late October 2009, and returning to seasonal baseline by January 2010 (Figures 1 and 2). During this time, >99% of viruses characterized were the 2009 pandemic influenza A (H1N1) virus (*11*). Data from epidemiologic studies conducted during the 2009 influenza A (H1N1) pandemic indicate that the risk for influenza complications among adults aged 19–64 years who had 2009 pandemic influenza A (H1N1) was greater than typically occurs for seasonal influenza (*12*). Influenza caused by 2009 pandemic influenza A (H1N1) virus is expected to continue to occur during future winter influenza seasons in the Northern and Southern Hemispheres, but whether 2009 pandemic influenza A (H1N1) viruses will replace or co-circulate with one or more of the two seasonal influenza A virus subtypes (seasonal H1N1 and H3N2) that have co-circulated since 1977 is unknown. Influenza viruses undergo frequent antigenic change as a result of point mutations and recombination events that occur during viral replication (i.e., antigenic drift). The extent of antigenic drift and evolution of 2009 pandemic influenza A (H1N1) virus strains in the future cannot be predicted.

Annual influenza vaccination is the most effective method for preventing influenza virus infection and its complications (*8*). Annual vaccination with the most up-to-date strains predicted on the basis of viral surveillance data is recommended. Influenza vaccine is recommended for all persons aged ≥6 months who do not have contraindications to vaccination.

FIGURE 1. Cumulative rate of hospitalizations during three influenza seasons, by age group — Emerging Infections Program, United States, 2007–2010



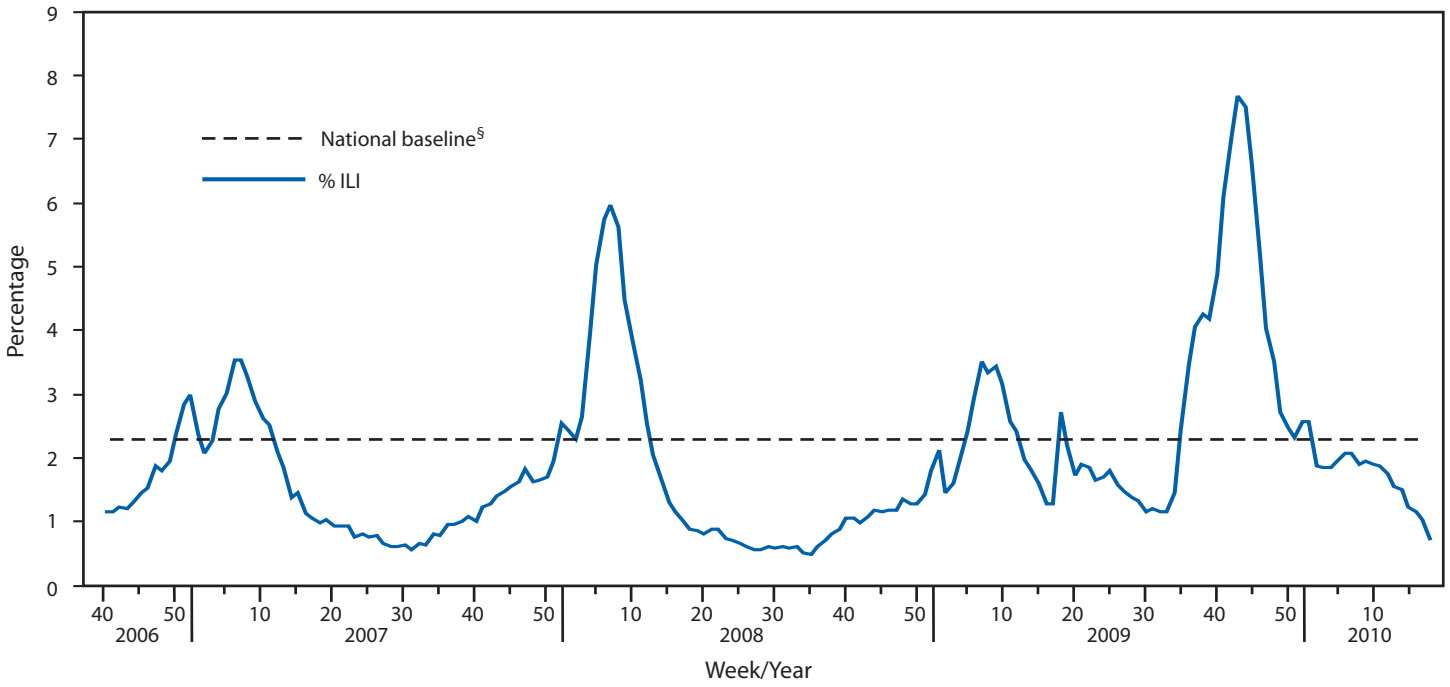
* 2009 Pandemic Influenza A(H1N1) hospitalization data from September 1, 2009–January 21, 2010.
† Per 10,000 population.

Trivalent inactivated influenza vaccine (TIV) can be used for any person aged ≥6 months, including those with high-risk conditions (Box). Live, attenuated influenza vaccine (LAIV) may be used for healthy nonpregnant persons aged 2–49 years. No preference is indicated for LAIV or TIV when considering vaccination of healthy nonpregnant persons aged 2–49 years. Because the safety or effectiveness of LAIV has not been established in persons with underlying medical conditions that confer a higher risk for influenza complications, these persons should be vaccinated only with TIV. Although vaccination coverage has increased in recent years for many groups recommended for routine vaccination, considerable room for improvement remains (*13*), and strategies to improve vaccination coverage in the medical home and in nonmedical settings should be implemented or expanded (*14*).

Antiviral medications are an adjunct to vaccination and are effective when administered as treatment and when used for chemoprophylaxis after an exposure to influenza virus. However, the emergence since 2005 of resistance to one or more of the four licensed antiviral agents (oseltamivir, zanamivir, amantadine, and rimantadine) among circulating strains has complicated antiviral treatment and chemoprophylaxis recommendations. CDC has revised recommendations for antiviral treatment and chemoprophylaxis of influenza periodically in response to new data on antiviral resistance patterns among circulating strains and risk factors for influenza complications (*15*). With few exceptions, 2009 pandemic influenza A (H1N1) virus strains that began circulating in April 2009 remained sensitive to oseltamivir (*16*).

Please note: An erratum has been published for this issue. To view the erratum, please click here.

FIGURE 2. Percentage of visits for influenza-like Illness (ILI)* reported by the U.S. Outpatient Influenza-like Illness Surveillance Network (ILINet),† by surveillance week — United States, October 1, 2006–May 1, 2010



* ILI is defined as fever (temperature of ≥100°F [≥37.8°C) and a cough and/or a sore throat in the absence of a known cause other than influenza.
† ILINet consists of approximately 2,400 health-care providers in 50 states reporting approximately 16 million patient visits each year.
§ The mean percentage of visits for ILI during noninfluenza weeks for the previous three seasons plus two standard deviations. A noninfluenza week is a week during which <10% of specimens tested positive for influenza.

Methods

CDC's Advisory Committee on Immunization Practices (ACIP) provides annual recommendations for the prevention and control of influenza. The ACIP Influenza Work Group (the Work Group)* meets every 2–4 weeks throughout the year to discuss newly published studies, review current guidelines, and consider revisions to the recommendations. As the Work Group reviews the annual recommendations for consideration by the full ACIP, its members discuss a variety of issues, including the burden of influenza illness; vaccine effectiveness, vaccine safety, and coverage in groups recommended for vaccination; feasibility; cost-effectiveness; and anticipated vaccine supply. Work Group members also request periodic updates on vaccine and antiviral production, supply, safety, and efficacy from vaccinologists, epidemiologists, and manufacturers. State and local vaccination program representatives are consulted. CDC's Influenza Division (available at http://www.cdc.gov/flu) provides influenza surveillance and antiviral resistance data. The Vaccines and Related Biological Products Advisory Committee provides advice on vaccine strain selection to the Food and Drug Administration (FDA), which selects the viral strains to be used in the annual trivalent influenza vaccines.

Published, peer-reviewed studies are the primary source of data used by ACIP in making recommendations for the prevention and control of influenza, but unpublished data that are relevant to issues under discussion also are considered. Among studies discussed or cited, those of greatest scientific quality and those that measure influenza-specific outcomes are the most influential. For example, population-based estimates of influenza disease burden supported by laboratory-confirmed influenza virus infection outcomes contribute the most specific data. The best evidence for vaccine or antiviral efficacy comes from randomized controlled trials that assess laboratory-confirmed influenza infections as an outcome measure and consider factors such as timing and intensity of influenza viruses' circulation and degree of match between vaccine strains and wild circulating strains (*17,18*). However, randomized controlled trials cannot be performed ethically in populations for which vaccination already is recommended, and in this context, observational studies that assess outcomes associated with laboratory-confirmed influenza infection also can provide important vaccine or antiviral safety and effectiveness data. Evidence for vaccine or antiviral safety also is provided

* A list of the members appears on page 62 of this report.

BOX. Summary of influenza vaccination recommendations, 2010

- All persons aged ≥6 months should be vaccinated annually.
- Protection of persons at higher risk for influenza-related complications should continue to be a focus of vaccination efforts as providers and programs transition to routine vaccination of all persons aged ≥6 months.
- When vaccine supply is limited, vaccination efforts should focus on delivering vaccination to persons who:
  - are aged 6 months–4 years (59 months);
  - are aged ≥50 years;
  - have chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, neurologic, hematologic, or metabolic disorders (including diabetes mellitus);
  - are immunosuppressed (including immunosuppression caused by medications or by human immunodeficiency virus);
  - are or will be pregnant during the influenza season;
  - are aged 6 months–18 years and receiving long-term aspirin therapy and who therefore might be at risk for experiencing Reye syndrome after influenza virus infection;
  - are residents of nursing homes and other chronic-care facilities;
  - are American Indians/Alaska Natives;
  - are morbidly obese (body-mass index ≥40);
  - are health-care personnel;
  - are household contacts and caregivers of children aged <5 years and adults aged ≥50 years, with particular emphasis on vaccinating contacts of children aged <6 months; and
  - are household contacts and caregivers of persons with medical conditions that put them at higher risk for severe complications from influenza.

by randomized controlled studies; however, the number of subjects in these studies often is inadequate to detect associations between vaccine and rare adverse events. The best way to assess the frequency of rare adverse events after vaccination is by controlled studies after vaccines are used widely in the population. These studies often use electronic medical records from large linked clinical databases and medical charts of persons who are identified as having a vaccine adverse event (*19–21*). Vaccine coverage data from a nationally representative, randomly selected population that include verification of vaccination through health-care record review are superior to coverage data derived from limited population samples or from self-reported vaccination status; however, the former rarely is obtained in vaccination coverage data for children aged ≥5 years (*22*). Finally, studies that assess vaccination program practices that improve vaccination coverage are most influential in formulating recommendations if the study design includes a nonintervention comparison group. In cited studies that included statistical comparisons, a difference was considered to be statistically significant if the p-value was <0.05 or the 95% confidence interval around an estimate of effect allowed rejection of the null hypothesis (i.e., no effect).

Data presented in this report were current as of June 29, 2010, and represent recommendations presented to the full ACIP and approved on February 24, 2010, and June 24, 2010. Modifications were made to the ACIP statement during the subsequent review process at CDC to update and clarify wording in the document. Vaccine recommendations apply only to persons who do not have contraindications to vaccine use (see Contraindications and Precautions for Use of TIV and Contraindications and Precautions for Use of LAIV). Further updates, if needed, will be posted at CDC's influenza website (http://www.cdc.gov/flu).

Primary Changes and Updates in the Recommendations

The 2010 recommendations include five principal changes or updates:

- Routine influenza vaccination is recommended for all persons aged ≥6 months. This represents an expansion of the previous recommendations for annual vaccination of all adults aged 19—49 years and is supported by evidence that annual influenza vaccination is a safe and effective preventive health action with potential benefit in all age groups. By 2009, annual vaccination was already recommended for an estimated 85% of the U.S. population, on the basis of risk factors for influenza-related complications or having close contact with a person at higher risk for influenza-related complications. The only group remaining that was not recommended for routine vaccination was healthy nonpregnant adults aged 18–49 years who did not have an occupational risk for infection and who were not close contacts of persons at higher risk for influenza-related complications. However, some adults who have influenza-related complications have no previously identified risk factors for influenza complications. In addition, some adults who have medical conditions

or age-related increases in their risk for influenza-related complications or another indication for vaccination are unaware that they should be vaccinated. Further support for expansion of annual vaccination recommendations to include all adults is based on concerns that 2009 pandemic influenza A (H1N1)-like viruses will continue to circulate during the 2010–11 influenza season and that a substantial proportion of young adults might remain susceptible to infection with this virus. Data from epidemiologic studies conducted during the 2009 pandemic indicate that the risk for influenza complications among adults aged 19–49 years is greater than is seen typically for seasonal influenza (*12,23,27*).

- As in previous recommendations, all children aged 6 months–8 years who receive a seasonal influenza vaccine for the first time should receive 2 doses. Children who received only 1 dose of a seasonal influenza vaccine in the first influenza season that they received vaccine should receive 2 doses, rather than 1, in the following influenza season. In addition, for the 2010–11 influenza season, children aged 6 months–8 years who did not receive at least 1 dose of an influenza A (H1N1) 2009 monovalent vaccine should receive 2 doses of a 2010–11 seasonal influenza vaccine, regardless of previous influenza vaccination history. Children aged 6 months–8 years for whom the previous 2009–10 seasonal or influenza A (H1N1) 2009 monovalent vaccine history cannot be determined should receive 2 doses of a 2010–11 seasonal influenza vaccine.
- The 2010–11 trivalent vaccines will contain A/California/7/2009 (H1N1)-like, A/Perth/16/2009 (H3N2)-like, and B/Brisbane/60/2008-like antigens. The influenza A (H1N1) vaccine virus is derived from a 2009 pandemic influenza A (H1N1) virus.
- A newly approved inactivated trivalent vaccine containing 60 mcg of hemagglutinin antigen per influenza vaccine virus strain (Fluzone High-Dose [sanofi pasteur]) is an alternative inactivated vaccine for persons aged ≥65 years. Persons aged ≥65 years can be administered any of the standard-dose TIV preparations or Fluzone High-Dose. Persons aged <65 years who receive inactivated influenza vaccine should be administered a standard-dose TIV preparation.
- Previously approved inactivated influenza vaccines that were approved for expanded age indications in 2009 include Fluarix (GlaxoSmithKline), which is now approved for use in persons aged ≥3 years, and Afluria (CSL Biotherapies), which is now approved for use in persons aged ≥6 months. A new inactivated influenza vaccine, Agriflu (Novartis), has been approved for persons aged ≥18 years.

Background and Epidemiology

Biology of Influenza

Influenza A and B are the two types of influenza viruses that cause epidemic human disease. Influenza A viruses are categorized into subtypes on the basis of two surface antigens: hemagglutinin and neuraminidase. During 1977–2010, influenza A (H1N1) viruses, influenza A (H3N2) viruses, and influenza B viruses have circulated globally. Influenza A subtypes and B viruses are separated further into groups on the basis of antigenic similarities. New influenza virus variants result from frequent antigenic change (i.e., antigenic drift) caused by point mutations and recombination events that occur during viral replication (*8*). Recent studies have explored the complex molecular evolution and epidemiologic dynamics of influenza A viruses (*28–30*).

New or substantially different influenza A subtypes have the potential to cause a pandemic when they are able to cause human illness and demonstrate efficient human-to-human transmission and when little or no previously existing immunity has been identified among humans (*8*). In April 2009, human infections with a novel influenza A (H1N1) virus were identified, and this virus subsequently caused a worldwide pandemic (*9*). The 2009 pandemic influenza A (H1N1) virus is derived from influenza A viruses that have circulated in swine during the past several decades and is antigenically distinct from human influenza A (H1N1) viruses in circulation since 1977. The 2009 pandemic influenza A (H1N) virus contains a combination of gene segments that had not been reported previously in animals or humans. The hemagglutination (HA) gene, which codes for the surface protein most important for immune response, is related most closely to the HA found in contemporary influenza viruses circulating among pigs. This HA gene apparently evolved from the avian-origin 1918 pandemic influenza H1N1 virus, which is thought to have entered human and swine populations at about the same time (*28*).

Currently circulating influenza B viruses are separated into two distinct genetic lineages (Yamagata and Victoria) but are not categorized into subtypes. Influenza B viruses undergo antigenic drift less rapidly than influenza A viruses. Influenza B viruses from both lineages have circulated in most recent influenza seasons (*31*).

Immunity to surface antigens, particularly hemagglutinin, reduces the likelihood of infection (*32*). Antibody against one influenza virus type or subtype confers limited or no protection against another type or subtype of influenza virus. Furthermore, antibody to one antigenic type or subtype of influenza virus might not protect against infection with a new antigenic variant of the same type or subtype (*33*). Frequent

emergence of antigenic variants through antigenic drift is the virologic basis for seasonal epidemics and is the reason for annually reassessing the need to change one or more of the recommended strains for influenza vaccines.

More dramatic changes, or antigenic shifts, occur less frequently. Antigenic shift occurs when a new subtype of influenza A virus appears and can result in the emergence of a novel influenza A virus with the potential to cause a pandemic. The 2009 pandemic influenza A (H1N1) virus is not a new subtype, but because most humans had no pre-existing antibody to key pandemic 2009 influenza A (H1N1) virus hemagglutinin epitopes, widespread transmission was possible (*28*).

Health-Care Use, Hospitalizations, and Deaths Attributed to Influenza

In the United States, annual epidemics of influenza typically occur during the fall or winter months, but the peak of influenza activity can occur as late as April or May. Influenza-related complications requiring urgent medical care, including hospitalizations or deaths, can result from the direct effects of influenza virus infection, from complications associated with age or pregnancy, or from complications of underlying cardiopulmonary conditions or other chronic diseases. Studies that have measured rates of a clinical outcome without a laboratory confirmation of influenza virus infection (e.g., respiratory illness requiring hospitalization during influenza season) to assess the effect of influenza can be difficult to interpret because of circulation of other respiratory pathogens (e.g., respiratory syncytial virus) during the same time as influenza viruses (*34–36*). However, increases in health-care provider visits for acute febrile respiratory illness occur each year during the time when influenza viruses circulate. Data from the U.S. Outpatient Influenza-like Illness Surveillance Network (ILINet) demonstrate the annual increase in physician visits for influenza-like illness (ILI)[†] and for each influenza season; for 2009, these data also indicated the increase in respiratory illness associated with circulation of 2009 pandemic influenza A (H1N1) virus during Spring 2009 and the resurgence of cases in Fall 2009 (Figure 2) (*37,38*).

In typical winter influenza seasons, an increase in deaths and hospitalizations is observed during periods when influenza viruses are circulating. Some persons whose hospitalization is attributed to invasive pneumococcal pneumonia are likely to have influenza as a co-pathogen, based on correlation between influenza activity and seasonal variations in pneumococcal pneumonia (*39*). The number of deaths or hospitalizations attributable at least partly to influenza can be estimated by applying modeling techniques to viral surveillance and national mortality or hospitalizations data and includes deaths and hospitalizations for which influenza infection is likely a contributor to mortality but not necessarily the sole cause of death (*6,7,40,41*).

Excess deaths and hospitalizations during influenza season that are likely to be caused at least partly by influenza are derived from the broad category of pulmonary and circulatory deaths or hospitalizations. Estimates that include only outcomes attributed to pneumonia and influenza underestimate the proportion of severe illnesses that are attributable at least partly to influenza because such estimates exclude deaths caused by exacerbations of underlying cardiac and pulmonary conditions that are associated with influenza infection (*6,7,40–42*).

During seasonal influenza epidemics from 1979–1980 through 2000–2001, the estimated annual overall number of influenza-associated hospitalizations in the United States ranged from approximately 55,000 to 431,000 per annual epidemic (mean: 226,000) (*7*). In the United States, the estimated number of influenza-associated deaths increased during 1990–1999. This increase was attributed in part to the substantial increase in the number of persons aged ≥65 years, including many who were at higher risk for death from influenza complications (*6*). When mortality data that included deaths attributable to both the pneumonia and influenza as well as the respiratory and circulatory categories were used as a basis for estimating the influenza burden, an average of approximately 19,000 influenza-associated deaths per influenza season occurred during 1976–1990 compared with an average of approximately 36,000 deaths per season during 1990–1999 (*6*). On the basis of data from the pneumonia and influenza category alone, an estimated annual average of 8,000 influenza-related deaths occurred. In addition, influenza A (H3N2) viruses, which have been associated with higher mortality (*43*), predominated in 90% of influenza seasons during 1990–1999 compared with 57% of seasons during 1976–1990 (*6*). From the 1990–91 influenza season through the 1998–99 season, the estimated annual number of deaths attributed to influenza ranged from 17,000 to 51,000 per epidemic (*6*). Estimates of mortality using a variety of different modeling techniques generally have been similar, although estimates for more recent years, when influenza A (H1N1) viruses have predominated more often, have been somewhat lower (*40*).

Influenza viruses cause disease among persons in all age groups (*1–5*). Rates of infection are highest among children, but the risks for complications, hospitalizations, and deaths from seasonal influenza are higher among adults aged ≥65 years, children aged <5 years, and persons of any age who

[†] ILI is defined as fever (temperature of ≥100°F [≥37.8°C) and a cough and/or a sore throat in the absence of a known cause other than influenza.

have medical conditions that place them at increased risk for complications from influenza (*1,4,5,44–47*). Estimated rates of influenza-associated hospitalizations and deaths varied substantially by age group in studies conducted during different seasonal influenza epidemics. During 1990–1999, estimated average rates of influenza-associated pulmonary and circulatory deaths per 100,000 persons were 0.4–0.6 among persons aged 0–49 years, 7.5 among persons aged 50–64 years, and 98.3 among persons aged ≥65 years (*6*).

During the 2009 influenza A (H1N1) pandemic, epidemiologic studies in multiple countries indicated that hospitalization rates and deaths among children and adults aged <65 years exceeded those observed during typical winter seasonal influenza epidemics (*12,23,25,48,49*). In one analysis, the mean age among persons who died in the United States during May–December 2009 and who had laboratory-confirmed influenza was 37 years. In contrast, the estimated mean age among persons who died from seasonal influenza during 1979–2001 was 76 years (*50*). The estimated number of hospitalizations and deaths among adults aged ≥65 years was below that observed in most seasonal epidemics. This difference was attributed to a lower risk for infection (*51*) associated with a higher prevalence of partial or full immunity among older persons, presumably as a result of exposures to antigenically similar influenza A viruses that circulated in the early-mid 20th century. One indication of some degree of preexisting immunity was the presence of cross-reacting antibody present among approximately one third of older adults (*52*), which has been attributed to similarities in the structure of the hemagglutinin protein among the 2009 H1N1 virus and those that circulated earlier in the 20th century (*53*).

Children

Among children aged <5 years, influenza-related illness is a common cause of visits to medical practices and emergency departments (EDs). During two influenza seasons (2002–03 and 2003–04), the percentage of visits among children aged <5 years with acute respiratory illness or fever caused by laboratory-confirmed influenza ranged from 10%–19% of medical office visits to 6%–29% of ED visits. On the basis of these data, the rate of visits to medical clinics for influenza was estimated to be 50–95 visits per 1,000 children, and the rate of visits to EDs was estimated to be 6–27 visits per 1,000 children (*54*). In a multiyear study in New York City that used viral surveillance data to estimate influenza strain-specific illness rates among ED visits, in addition to the expected variation by season and age group, influenza B epidemics were determined to be an important cause of illness among school-aged children in several seasons, and annual epidemics of both influenza A and B peaked among school-aged children before other age groups (*55*). Retrospective studies using medical records data have demonstrated similar rates of illness among children aged <5 years during other influenza seasons (*45,56,57*). During an influenza season, seven to 12 additional outpatient visits and five to seven additional antibiotic prescriptions per 100 children aged <15 years have been estimated compared with periods when influenza viruses are not circulating, with rates decreasing with increasing age of the child (*57*). During 1993–2004 in the Boston area, the rate of ED visits for respiratory illnesses that were attributed to influenza virus on the basis of viral surveillance data among children aged ≤7 years during the winter respiratory illness season ranged from 22.0 per 1,000 children aged 6–23 months to 5.4 per 1,000 children aged 5–7 years (*58*).

Estimates of rates of influenza-associated hospitalization are substantially higher among infants and children aged <2 years compared with older children and are similar to rates for other groups considered at higher risk for influenza-related complications (*59–64*), including persons aged ≥65 years (*57,61*). During 1979–2001, the estimated rate of influenza-associated hospitalizations among children aged <5 years in the United States was 108 hospitalizations per 100,000 person-years, based on data from a national sample of hospital discharges of influenza-associated hospitalizations (*7*). Recent population-based studies that measured hospitalization rates for laboratory-confirmed influenza in young children have documented hospitalization rates that are similar to or higher than rates derived from studies that analyzed hospital discharge data (*54,56,63,65,66*). Annual hospitalization rates for laboratory-confirmed influenza decrease with increasing age, ranging from 240–720 per 100,000 children aged <6 months to approximately 20 per 100,000 children aged 2–5 years (*54*). Hospitalization rates for children aged <5 years with high-risk medical conditions are approximately 250–500 per 100,000 children (*45,47,67*).

Influenza-associated deaths are uncommon among children. An estimated annual average of 92 influenza-associated deaths (0.4 deaths per 100,000 persons) occurred among children aged <5 years during the 1990s compared with 32,651 deaths (98.3 per 100,000 persons) among adults aged ≥65 years (*6*). Of 153 laboratory-confirmed influenza-related pediatric deaths reported during the 2003–04 influenza season, 96 (63%) deaths occurred among children aged <5 years and 61 (40%) among children aged <2 years. Among the 149 children who died and for whom information on underlying health status was available, 100 (67%) did not have an underlying medical condition that was an indication for vaccination at that time (*68*). In California during the 2003–04 and 2004–05 influenza seasons, 51% of children aged <18 years with laboratory-confirmed influenza who died and 40% of those who required

admission to an intensive care unit had no underlying medical conditions (*69*). These data indicate that although children with risk factors for influenza complications are at higher risk for death, the majority of pediatric deaths occur among children with no known high-risk conditions.

Since 2004, death associated with laboratory-confirmed influenza virus infection among children (defined as persons aged <18 years) has been a nationally reportable condition. During 2004–2005, the annual number of seasonal influenza-associated deaths among children aged <18 years reported to CDC ranged from 47 during 2004–05 to 88 during 2007–08 (*70*). During April 2009–March 2010, over 300 deaths attributable to laboratory-confirmed 2009 H1N1 influenza among children, the majority of whom had one or more underlying medical conditions, were reported to CDC in the United States, and over 1,000 deaths are estimated to have occurred (*71*; CDC, unpublished data, 2010).

Deaths among children that have been attributed to co-infection with influenza and *Staphylococcus aureus*, particularly methicillin-resistant *S. aureus* (MRSA), have increased (*38,72*), and illness severity of co-infection is increased compared with influenza alone (*73*). The reason for this increase in co-infections has not been established but might reflect an increasing prevalence within the general population of colonization with MRSA strains, some of which carry certain virulence factors (*74,75*).

Adults

Among healthy younger adults, illness caused by seasonal influenza is typically not severe and rarely results in hospitalization, compared with children aged <5 years, adults aged ≥65 years, pregnant women, or persons with chronic medical conditions. However, illness burden among healthy adults aged 19–49 years is an important cause of outpatient medical visits and worker absenteeism. The impact of influenza varies considerably by season, making estimates of the attack rate in healthy younger adults difficult. In most studies, attack rates have varied from 2% to 10% annually, and influenza has been estimated to cause 0.6–2.5 workdays lost per illness (*76–80*). In one economic analysis, the average annual burden of seasonal influenza among adults aged 18–49 years who did not have a medical condition that conferred a higher risk for influenza complications was estimated to include approximately 5 million illnesses, 2.4 million outpatient visits, 32,000 hospitalizations, and 680 deaths (*78*).

Hospitalization rates during typical influenza seasons are substantially increased for persons aged ≥65 years compared with younger age groups. One retrospective analysis based on data from managed-care organizations collected during 1996–2000 estimated that the risk during influenza season among persons aged ≥65 years with underlying conditions that put them at risk for influenza-related complications (i.e., one or more of the conditions listed as indications for vaccination) was approximately 560 influenza-associated hospitalizations per 100,000 persons compared with approximately 190 per 100,000 healthy persons aged ≥65 years. Persons aged 50–64 years who have underlying medical conditions also were at substantially increased risk for hospitalizations during influenza season compared with healthy adults aged 50–64 years (*44*).

Influenza is an important contributor to the annual increase in deaths attributed to pneumonia and influenza that is observed during the winter months. During 1976–2001, an estimated yearly average of 32,651 (90%) influenza-related deaths occurred among adults aged ≥65 years, with the risk for an influenza-related death highest in the oldest age groups (*6*). Persons aged ≥85 years were 16 times more likely to die from an influenza-related illness compared with persons aged 65–69 years (*6*).

During the 2009 H1N1 pandemic, adults aged <65 years were at higher risk for influenza-related complications (*23,81,82*), particularly those aged 50–64 years who had underlying medical conditions, compared with typical influenza seasons. The distribution of hospitalizations by age group differed from usual seasonal influenza patterns during 2009–10, with more hospitalizations among younger age groups and fewer among adults aged ≥65 years (Figure 1). Hospitalization rates exceeded those seen in any recent influenza season among adults aged ≤65 years (*26*). Pneumonia with evidence of invasive bacterial co-infection has been reported in approximately one third of fatal cases in autopsy studies (*83*). In one study of critically ill adults who required mechanical ventilation, *Streptococcus pneumoniae* pneumonia at admission was an independent risk factor for death (*84*). In addition, obesity (body-mass index [BMI] ≥30) and particularly morbid obesity (BMI ≥40) appeared to be risk factors for hospitalization and death in some studies (*23,24,81,85,86*). Additional studies are needed to determine whether obesity is a risk factor specific to the 2009 H1N1-like influenza viruses or a previously unrecognized risk factor for influenza-related complications caused by other influenza viruses. Other epidemiologic features of the 2009 H1N1 pandemic underscored racial and ethnic disparities in the risk for influenza-related complications among adults, including higher rates of hospitalization for blacks and a disproportionate number of deaths among American Indians/Alaska Natives and indigenous populations in other countries (*87–91*). These disparities might be attributable in part to the higher prevalence of underlying medical conditions or disparities in medical care among these racial/ethnic groups (*92,93*).

The duration of influenza symptoms is prolonged and the severity of influenza illness increased among persons with

human immunodeficiency virus (HIV) infection (*94–98*). A retrospective study of women aged 15–64 years enrolled in Tennessee's Medicaid program determined that the attributable risk for cardiopulmonary hospitalizations among women with HIV infection was higher during influenza seasons than it was either before or after influenza was circulating. The risk for hospitalization was higher for HIV-infected women than it was for women with other underlying medical conditions (*99*). Another study estimated that the risk for influenza-related death was 94–146 deaths per 100,000 persons with acquired immune deficiency syndrome (AIDS) compared with 0.9–1.0 deaths per 100,000 persons aged 25–54 years and 64–70 deaths per 100,000 persons aged ≥65 years in the general population (*100*).

Influenza-related excess deaths among pregnant women were reported during the pandemics of 1918–1919, 1957–1958, and 2009–2010 (*48,101–106*). Severe infections among postpartum women (those delivered within the previous 2 weeks) also were observed in the 2009–10 pandemic (*48,107,108*). Case reports and several epidemiologic studies also indicate that pregnancy increases the risk for seasonal influenza complications for the mother (*109–114*). The majority of studies that have attempted to assess the effect of influenza on pregnant women have measured changes in excess hospitalizations for respiratory illness during influenza season but not laboratory-confirmed influenza hospitalizations. Pregnant women have an increased number of medical visits for respiratory illnesses during influenza season compared with nonpregnant women (*115*). Hospitalized pregnant women with respiratory illness during influenza season have increased lengths of stay compared with hospitalized pregnant women without respiratory illness. Rates of hospitalization for respiratory illness were twice as common during influenza season (*116*). A retrospective cohort study of approximately 134,000 pregnant women conducted in Nova Scotia during 1990–2002 compared medical record data for pregnant women to data from the same women during the year before pregnancy. Among pregnant women, 0.4% were hospitalized, and 25% visited a clinician during pregnancy for a respiratory illness. The rate of third-trimester hospital admissions during the influenza season was five times higher than the rate during the influenza season in the year before pregnancy and more than twice as high as the rate during the noninfluenza season. An excess of 1,210 hospital admissions in the third trimester per 100,000 pregnant women with comorbidities and of 68 admissions per 100,000 women without comorbidities was reported (*117*). In one study, pregnant women with hospitalizations for respiratory symptoms did not have an increase in adverse perinatal outcomes or delivery complications (*118*); another study indicated an increase in delivery complications, including fetal distress, preterm labor, and cesarean delivery. However, infants born to women with laboratory-confirmed influenza during pregnancy do not have higher rates of low birth weight, congenital abnormalities, or lower Apgar scores compared with infants born to uninfected women (*109,119*).

In a case series conducted during the 2009 H1N1 pandemic, 56 deaths were reported among 280 women admitted to intensive care units (*120*). Among the deaths, 36 (64%) occurred in the third trimester. Pregnant women who received treatment >4 days after symptom onset were more likely than those treated within 2 days after symptom onset to be admitted to an intensive care unit (57% and 9%, respectively; relative risk [RR]: 6.0; 95% CI = 3.5–10.6) (*120*).

Options for Controlling Influenza

The most effective strategy for preventing influenza is annual vaccination. Strategies that focus on providing routine vaccination to persons at higher risk for influenza complications have long been recommended, although coverage among the majority of these groups remains low. Routine vaccination of certain persons (e.g., children, contacts of persons at risk for influenza complications, and health-care personnel [HCP]) who serve as a source of influenza virus transmission might provide additional protection to persons at risk for influenza complications and reduce the overall influenza burden. However, coverage levels among these persons need to be increased before effects on transmission can be measured reliably. Antiviral medications can be used for chemoprophylaxis and have been demonstrated to prevent influenza illness. When used for treatment, antiviral medications have been demonstrated to reduce the severity and duration of illness, particularly if used within the first 48 hours after illness onset. However, antiviral medications are adjuncts to vaccine in the prevention and control of influenza, and primary prevention through annual vaccination is the most effective and efficient prevention strategy. Despite recommendations to use antiviral medications to treat hospitalized patients with suspected influenza, antiviral drugs are underused (*121*).

Reductions in detectable influenza A viruses on hands after handwashing have been demonstrated, and handwashing has been demonstrated to reduce the overall incidence of respiratory diseases (*122–124*). Nonpharmacologic interventions (e.g., frequent handwashing and improved respiratory hygiene) are reasonable and inexpensive. However, the impact of hygiene interventions such as handwashing on influenza virus transmission is not well understood, and hygiene measures should not be advocated as a replacement or alternative to specific prevention measures such as vaccination. Few data are available to assess the effects of community-level respiratory

Please note: An erratum has been published for this issue. To view the erratum, please click here.

disease mitigation strategies (e.g., closing schools, avoiding mass gatherings, or using respiratory protection) on reducing influenza virus transmission during typical seasonal influenza epidemics (*125–127*). An interventional trial among university students indicated that students living in dormitories who were asked to use surgical face masks, given an alcohol-based hand sanitizer, and provided with education about mask use and hand hygiene during influenza season had substantially lower rates of ILI compared with students in dormitories for whom no intervention was recommended. However, neither face mask nor hand sanitizer use alone was associated with statistically significant reduction in ILI (*128*). During the 2009 pandemic, one study indicated that having members of households in which an influenza case was identified discuss ways to avoid transmission was associated with a significant reduction in the frequency of additional cases after one household member became ill, suggesting that education measures might be an effective way to reduce secondary transmission (*129*). Limited data suggest that transmission of seasonal influenza or ILI among household members can be reduced if household contacts use a surgical face mask or implement hand washing early in the course of an ill index case patient's illness (*130,131*). However, these interventions might supplement use of vaccine as a means to reduce influenza transmission or provide some protection when vaccine is not available (*130–132*).

Influenza Vaccine Efficacy, Effectiveness, and Safety

Evaluating Influenza Vaccine Efficacy and Effectiveness Studies

The efficacy (i.e., prevention of illness among vaccinated persons in controlled trials) and effectiveness (i.e., prevention of illness in vaccinated populations) of influenza vaccines depend in part on the age and immunocompetence of the vaccine recipient, the degree of similarity between the viruses in the vaccine and those in circulation (see Effectiveness of Influenza Vaccination When Circulating Influenza Virus Strains Differ from Vaccine Strains), and the outcome being measured. Influenza vaccine efficacy and effectiveness studies have used multiple possible outcome measures, including the prevention of medically attended acute respiratory illness (MAARI), laboratory-confirmed influenza virus illness, influenza or pneumonia-associated hospitalizations or deaths, or seroconversion. Efficacy or effectiveness for more specific outcomes such as laboratory-confirmed influenza typically will be higher than for less specific outcomes such as MAARI because the causes of MAARI include infections with other pathogens that influenza vaccination would not be expected to prevent (*133*). Observational studies that compare less-specific outcomes among vaccinated populations to those among unvaccinated populations are subject to biases that are difficult to control for during analyses. For example, an observational study that determines that influenza vaccination reduces overall mortality might be biased if healthier persons in the study are more likely to be vaccinated (*134,135*). Randomized controlled trials that measure laboratory-confirmed influenza virus infections as the outcome are the most persuasive evidence of vaccine efficacy, but such trials cannot be conducted ethically among groups recommended to receive vaccine annually.

Influenza Vaccine Composition

Both LAIV and TIV contain strains of influenza viruses that are equivalent antigenically to the annually recommended strains: one influenza A (H3N2) virus, one influenza A (H1N1) virus, and one influenza B virus. Each year, one or more virus strains in the vaccine might be changed on the basis of global surveillance for influenza viruses and the emergence and spread of new strains. The 2010–11 trivalent vaccines will contain A/California/7/2009 (H1N1)-like, A/Perth/16/2009 (H3N2)-like, and B/Brisbane/60/2008-like antigens. The A/California/7/2009 (H1N1)-like antigen is derived from a pandemic 2009 influenza A (H1N1) virus and is the same vaccine antigen used in the influenza A (H1N1) 2009 monovalent vaccines. The A/Perth/16/2009 (H3N2)-like antigen is different from the H3N2-like antigen recommended for the 2009–10 northern hemisphere seasonal influenza vaccine. The influenza B vaccine strain will remain B/Brisbane/16/2008 and is not changed compared with the 2009–10 northern hemisphere seasonal influenza vaccine (*136*). Viruses for currently licensed TIV and LAIV preparations are grown in chicken eggs. Either vaccine is administered annually to provide optimal protection against influenza virus infection (Table 1). Both TIV and LAIV are widely available in the United States. Although both types of vaccines are expected to be effective, the vaccines differ in several respects (Table 1). None of the influenza vaccines licensed in the United States contains an adjuvant.

Major Differences Between TIV and LAIV

TIV contains inactivated viruses and thus cannot cause influenza. LAIV contains live attenuated influenza viruses that have the potential to cause mild signs or symptoms related to vaccine virus infection (e.g., rhinorrhea, nasal congestion, fever, or sore throat). LAIV is administered intranasally by sprayer, whereas TIV is administered intramuscularly by injection. LAIV is licensed for use among nonpregnant persons aged

TABLE 1. Live, attenuated influenza vaccine (LAIV) compared with inactivated influenza vaccine (TIV) for seasonal influenza, U.S. formulations

Factor	LAIV	TIV
Route of administration	Intranasal spray	Intramuscular injection
Type of vaccine	Live virus	Killed virus
No. of included virus strains	3 (2 influenza A, 1 influenza B)	3 (2 influenza A, 1 influenza B)
Vaccine virus strains updated	Annually	Annually
Frequency of administration	Annually*	Annually*
Approved age	Persons aged 2–49 yrs†	Persons aged ≥6 mos§
Interval between 2 doses recommended for children aged ≥6 mos–8 yrs who are receiving influenza vaccine for the first time	≥4 wks	≥4 wks
Can be given to persons with medical risk factors for influenza-related complications†	No	Yes
Can be given to children with asthma or children aged 2–4 yrs with wheezing in the past yr¶	No	Yes
Can be administered to family members or close contacts of immunosuppressed persons not requiring a protected environment	Yes	Yes
Can be administered to family members or close contacts of immunosuppressed persons requiring a protected environment (e.g., hematopoietic stem cell transplant recipient)	No	Yes
Can be administered to family members or close contacts of persons at higher risk including pregnant women, but not severely immunosuppressed	Yes	Yes
Can be administered simultaneously with other vaccines	Yes**	Yes††
If not administered simultaneously, can be administered within 4 weeks of another live vaccine	Prudent to space ≥4 wks apart	Yes
If not administered simultaneously, can be administered within 4 wks of an inactivated vaccine	Yes	Yes

* Children aged ≥6 months–8 years who have never received a seasonal influenza vaccine before or who did not receive at least 1 dose of an influenza A (H1N1) 2009 monovalent vaccine should receive 2 doses, spaced ≥4 weeks apart. Those children aged 6 months–8 years who were vaccinated for the first time in the 2009–10 season with the seasonal 2009–10 vaccine but who received only 1 dose of seasonal influenza vaccine should receive 2 doses in the following year, spaced ≥4 wks apart.

† Persons at higher risk for complications of influenza infection because of underlying medical conditions should not receive LAIV. Such persons include those who have chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, neurologic, hematologic, or metabolic (including diabetes mellitus) disorders; those who are immunosuppressed (including immunosuppression caused by medications or by human immunodeficiency virus); those who are or will be pregnant during the influenza season; those aged 6 months–18 years and receiving long-term aspirin therapy and who therefore might be at risk for experiencing Reye syndrome after influenza virus infection; and residents of nursing homes and other chronic-care facilities.

§ Approval varies by formulation. Fluzone (sanofi pasteur) and Afluria (CSL Biotherapies) have been approved previously for use in children as young as age 6 months. Fluzone High-Dose is approved for use in persons aged ≥65 years. Immunization providers should check Food and Drug Administration–approved prescribing information for 2010–11 influenza vaccines for the most updated information.

¶ Clinicians and vaccination programs should screen for possible reactive airways diseases when considering use of LAIV for children aged 2–4 years and should avoid use of this vaccine in children with asthma or a recent wheezing episode. Health-care providers should consult the medical record, when available, to identify children aged 2–4 years with asthma or recurrent wheezing that might indicate asthma. In addition, to identify children who might be at greater risk for asthma and possibly at increased risk for wheezing after receiving LAIV, parents or caregivers of children aged 2–4 years should be asked: "In the past 12 months, has a health-care provider ever told you that your child had wheezing or asthma?" Children whose parents or caregivers answer "yes" to this question and children who have asthma or who had a wheezing episode noted in the medical record within the preceding 12 months, should not receive LAIV.

** LAIV coadministration has been evaluated systematically only among children aged 12–15 months who received with measles, mumps and rubella vaccine or varicella vaccine.

†† Inactivated influenza vaccine coadministration has been evaluated systematically only among adults who received pneumococcal polysaccharide or zoster vaccine.

2–49 years; safety has not been established in persons with underlying medical conditions that confer a higher risk for influenza complications. TIV is licensed for use among persons aged ≥6 months, including those who are healthy and those with chronic medical conditions (Table 1). During the preparation of TIV, the vaccine viruses are made noninfectious (i.e., inactivated or killed) (*8*). Only subvirion and purified surface antigen preparations of TIV (often referred to as "split" and subunit vaccines, respectively) are available in the United States. Standard-dose TIV preparations contain 7.5 mcg HA antigen per vaccine strain (for children aged <36 months) or 15 mcg of HA antigen (for persons aged ≥36 months) per vaccine strain (i.e., 22.5 mcg or 45 mcg total HA antigen). A newly licensed higher dose TIV (60 mcg per vaccine strain or 180 mcg total HA antigen) was approved recently for persons aged ≥65 years (Fluzone High-Dose, Sanofi pasteur).

Correlates of Protection after Vaccination

Immune correlates of protection against influenza infection after vaccination include serum hemagglutination inhibition antibody and neutralizing antibody (*32,137*). Increased levels of antibody induced by vaccination decrease the risk for illness caused by strains that are similar antigenically to those strains of the same type or subtype included in the vaccine (*138–141*). The majority of healthy children and adults have high titers of antibody after vaccination (*139,142*). Although immune correlates such as achievement of certain antibody titers after vaccination correlate well with immunity on a population level, the significance of reaching or failing to reach a certain antibody threshold (typically defined as a hemagglutination titer of 1:32 or 1:40) is not well understood on the individual level. Other immunologic correlates of protection that might best indicate

clinical protection after receipt of an intranasal vaccine such as LAIV (e.g., mucosal antibody) are more difficult to measure (*143,144*). Laboratory measurements that correlate with protective immunity induced by LAIV have been described, including measurement of cell-mediated immunity with ELISPOT assays that measure gamma-interferon (*143*).

Duration of Immunity

The recommended composition of influenza vaccines changes in most seasons, with one or more vaccine strains replaced annually to provide better protection against wild-type viruses that are likely to circulate. However, evidence from clinical trials suggests that protection against viruses that are similar antigenically to those contained in the vaccine extends for at least 6–8 months. Three years after vaccination with the A/Hong Kong/68 vaccine, vaccine effectiveness was 67% for prevention of influenza caused by the A/Hong Kong/68 virus (*145*). In randomized trials conducted among healthy college students, immunization with TIV provided 92% and 100% efficacy against influenza H3N2 and H1N1 illnesses, respectively, during the first year, and a 68% reduction against H1N1 illness during the second year (when the predominant circulating virus was H1N1) without revaccination (*146*). In a similar study of young adults in 1986–1987, TIV reduced influenza A (H1N1) illness 75% in the first year, H3N2 illness 45% in the second year, and H1N1 illness 61% in the third year after immunization (*146*). Serum anti-influenza antibodies and nasal IgA elicited by vaccination remain detectable in children vaccinated with LAIV for more than 1 year (*147*). In one community-based nonrandomized open label trial, continued protection from MAARI during the 2000–01 influenza season was demonstrated in children who received only a single dose of LAIV during the 1999–2000 season (*148*).

Adults aged ≥65 years typically have a diminished immune response to influenza vaccination compared with young healthy adults, suggesting that immunity might be of shorter duration (although still extending through one influenza season) (*149,150*). However, a review of the published literature concluded that no clear evidence existed that immunity declined more rapidly in the elderly (*151*), and additional vaccine doses during the same season do not increase the antibody response. One study that measured the proportion of persons who retained seroprotective levels of anti-influenza antibody declined in all age groups, including those aged ≥65 years, within 1 year of vaccination. However, the proportion in each age group that retained seroprotective antibody levels remained above standards typically used for vaccine licensure for seasonal influenza A (H1N1) and influenza A (H3N2) in all age groups. In this study, anti-influenza B antibody levels declined more quickly, but remained elevated well above licensure threshold for at least 6 months in all age groups (*152*). The frequency of breakthrough infections is not known to be higher among those who were vaccinated early in the season. Infections among the vaccinated elderly might be more likely related to an age-related reduction in ability to respond to vaccination rather than reduced duration of immunity.

Immunogenicity, Efficacy, and Effectiveness of TIV

Children

Children aged ≥6 months typically have protective levels of anti-influenza antibody against specific influenza virus strains after receiving the recommended number of doses of seasonal inactivated influenza vaccine (*137,142,153–157).* Immunogenicity studies using the influenza A (H1N1) 2009 monovalent vaccine indicated that >90% of children aged ≥9 years responded to a single dose with anti-influenza antibody levels that are considered to be protective. Young children had inconsistent responses to a single dose of the influenza A (H1N1) 2009 monovalent vaccine across studies, with 20% of children aged 6–35 months responding to a single dose with protective anti-influenza antibody levels. However, in all studies, 80%–95% of vaccinated infants, children, and adolescents developed protective anti-influenza antibody levels to the 2009 H1N1 influenza virus after 2 doses (*158–160*; National Institutes of Health, unpublished data, 2010).

In most seasons, one or more seasonal vaccine antigens are changed compared with the previous season. In consecutive years when vaccine antigens change, children aged <9 years who received only 1 dose of vaccine in their first year of vaccination are less likely to have protective antibody responses when administered only a single dose during their second year of vaccination compared with children who received 2 doses in their first year of vaccination (*161–163*).

When the vaccine antigens do not change from one season to the next, priming children aged 6–23 months with a single dose of vaccine in the spring followed by a dose in the fall engenders similar antibody responses compared with a regimen of 2 doses in the fall (*164*). However, one study conducted during a season when the vaccine antigens did not change compared with the previous season estimated 62% effectiveness against ILI for healthy children who had received only 1 dose in the previous influenza season and only 1 dose in the study season compared with 82% for those who received 2 doses separated by ≥4 weeks during the study season (*165*).

The antibody response among children at higher risk for influenza-related complications (e.g., children with chronic

medical conditions) might be lower than those reported typically among healthy children (*166,167*). However, antibody responses among children with asthma are similar to those of healthy children and are not substantially altered during asthma exacerbations requiring short-term prednisone treatment (*168*).

Vaccine effectiveness studies also have indicated that 2 doses are needed to provide adequate protection during the first season that young children are vaccinated. Among children aged <5 years who have never received influenza vaccine previously or who received only 1 dose of influenza vaccine in their first year of vaccination, vaccine effectiveness is lower compared with children who received 2 doses in their first year of being vaccinated. Two large retrospective studies of young children who had received only 1 dose of TIV in their first year of being vaccinated determined that no decrease was observed in ILI-related office visits compared with unvaccinated children (*165,169*). Similar results were reported in a case-control study of children aged 6–59 months in which laboratory-confirmed influenza was the outcome measured (*170*). These results, along with the immunogenicity data indicating that antibody responses are substantially higher when young children are given 2 doses, are the basis for the recommendation that all children aged 6 months–8 years who are being vaccinated for the first time should receive 2 vaccine doses separated by ≥4 weeks.

Estimates of vaccine efficacy or effectiveness among children aged ≥6 months have varied by season and study design. In a randomized trial conducted during five influenza seasons (1985–1990) in the United States among children aged 1–15 years, annual vaccination reduced laboratory-confirmed influenza A substantially (77%–91%) (*139*). A limited 1-year placebo-controlled study reported vaccine efficacy against laboratory-confirmed influenza illness of 56% among healthy children aged 3–9 years and 100% among healthy children and adolescents aged 10–18 years (*171*). A randomized, double-blind, placebo-controlled trial conducted during two influenza seasons among children aged 6–24 months indicated that efficacy was 66% against culture-confirmed influenza illness during the 1999–00 influenza season but did not reduce culture-confirmed influenza illness substantially during the 2000–01 influenza season (*172*).

A case-control study conducted during the 2003–04 season indicated vaccine effectiveness of 49% against laboratory-confirmed influenza (*170*). An observational study among children aged 6–59 months with laboratory-confirmed influenza compared with children who tested negative for influenza reported vaccine effectiveness of 44% in the 2003–04 influenza season and 57% during the 2004–05 season (*173*). Partial vaccination (only 1 dose for children being vaccinated for the first time) was not effective in either study. During an influenza season (2003–04) with a suboptimal vaccine match, a retrospective cohort study conducted among approximately 30,000 children aged 6 months–8 years indicated vaccine effectiveness of 51% against medically attended, clinically diagnosed pneumonia or influenza (i.e., no laboratory confirmation of influenza) among fully vaccinated children and 49% among approximately 5,000 children aged 6–23 months (*169*). Another retrospective cohort study of similar size conducted during the same influenza season in Denver but limited to healthy children aged 6–21 months estimated clinical effectiveness of 2 TIV doses to be 87% against pneumonia or influenza-related office visits (*165*). Among children, TIV effectiveness might increase with age (*139,174*). A systematic review of published studies estimated vaccine effectiveness at 59% for children aged >2 years but concluded that additional evidence was needed to demonstrate effectiveness among children aged 6 months–2 years (*175*).

Because of the recognized influenza-related disease burden among children with other chronic diseases or immunosuppression and the long-standing recommendation for vaccination of these children, randomized placebo-controlled studies to study efficacy in these children have not been conducted. In a nonrandomized controlled trial among children aged 2–6 years and 7–14 years who had asthma, vaccine efficacy was 54% and 78% against laboratory-confirmed influenza type A infection and 22% and 60% against laboratory-confirmed influenza type B infection, respectively. Vaccinated children aged 2–6 years with asthma did not have substantially fewer type B influenza virus infections compared with the control group in this study (*176*). The association between vaccination and prevention of asthma exacerbations is unclear. Vaccination was demonstrated to provide protection against asthma exacerbations in some studies (*177,178*).

TIV has been demonstrated to reduce acute otitis media in some studies. Two studies have reported that TIV decreases the risk for influenza-related otitis media by approximately 30% among children with mean ages of 20 and 27 months, respectively (*179,180*). However, a large study conducted among children with a mean age of 14 months indicated that TIV was not effective against acute otitis media (*172*). Influenza vaccine effectiveness against a nonspecific clinical outcome such as acute otitis media, which is caused by a variety of pathogens and is not typically diagnosed using influenza virus culture, would be expected to be relatively low.

Adults Aged <65 Years

One dose of TIV is highly immunogenic in healthy adults aged <65 years. Limited or no increase in antibody response is reported among adults when a second dose is administered

during the same season (*181–183*). The influenza A (H1N1) 2009 monovalent vaccines were also highly immunogenic; >90% of adults developed levels of anti-influenza antibody considered to be protective (*160,184*). When the vaccine and circulating viruses are antigenically similar, TIV prevents laboratory-confirmed influenza illness among approximately 70%–90% of healthy adults aged <65 years in randomized controlled trials (*77,80,185–187*). Vaccination of healthy adults also has resulted in decreased work absenteeism and decreased use of health-care resources, including use of antibiotics, when the vaccine and circulating viruses are well-matched (*77,185,186*). Efficacy or effectiveness against laboratory-confirmed influenza illness was substantially lower in studies conducted during different influenza seasons when the vaccine strains were antigenically dissimilar to the majority of circulating strains (*77,80,180,182,185,186*). However, effectiveness among healthy adults against influenza-related hospitalization, measured in the most recent of these studies, was 90% (*188*).

In certain studies, persons with certain chronic diseases have lower serum antibody responses after vaccination compared with healthy young adults and can remain susceptible to influenza virus infection and influenza-related upper respiratory tract illness (*189–191*). Vaccine effectiveness among adults aged <65 years who are at higher risk for influenza complications typically is lower than that reported for healthy adults. In a case-control study conducted during the 2003–04 influenza season, when the vaccine was a suboptimal antigenic match to many circulating virus strains, effectiveness for prevention of laboratory-confirmed influenza illness among adults aged 50–64 years with high-risk conditions was 48% compared with 60% for healthy adults (*188*). Effectiveness against hospitalization among adults aged 50–64 years with high-risk conditions was 36% compared with 90% effectiveness among healthy adults in that age range (*188*). A randomized controlled trial among adults in Thailand with chronic obstructive pulmonary disease (median age: 68 years) indicated a vaccine effectiveness of 76% in preventing laboratory-confirmed influenza during a season when viruses were well-matched to vaccine viruses. Effectiveness did not decrease with increasing severity of underlying lung disease (*192*).

Few randomized controlled trials have studied the effect of influenza vaccination on noninfluenza outcomes. A controlled trial conducted in Argentina among 301 adults hospitalized with myocardial infarction or undergoing angioplasty for cardiovascular disease (56% of whom were aged ≥65 years) who were randomized to receive influenza vaccine or no vaccine indicated that a substantially lower percentage (6%) of cardiovascular deaths occurred among vaccinated persons at 1 year after vaccination compared with unvaccinated persons (17%) (*193*). A randomized, double-blind, placebo-controlled study conducted in Poland among 658 persons with coronary artery disease indicated that significantly fewer vaccinated persons had a cardiac ischemic event during the 9 months of follow up compared with unvaccinated persons ($p<0.05$) (*194*).

Observational studies that have measured clinical endpoints without laboratory confirmation of influenza virus infection typically have demonstrated substantial reductions in hospitalizations or deaths among adults with risk factors for influenza complications. For example, in a case-control study conducted during 1999–2000 in Denmark among adults aged <65 years with underlying medical conditions, vaccination reduced deaths attributable to any cause 78% and reduced hospitalizations attributable to respiratory infections or cardiopulmonary diseases 87% (*195*). A benefit was reported after the first vaccination and increased with subsequent vaccinations in subsequent years (*196*). Among patients with diabetes mellitus, vaccination was associated with a 56% reduction in any complication, a 54% reduction in hospitalizations, and a 58% reduction in deaths (*197*). Certain experts have noted that the substantial effects on morbidity and mortality among those who received influenza vaccination in these observational studies should be interpreted with caution because of the difficulties in ensuring that those who received vaccination had similar baseline health status as those who did not (*134,135*). One meta-analysis of published studies concluded that evidence was insufficient to demonstrate that persons with asthma benefit from vaccination (*198*). However, a meta-analysis that examined effectiveness among persons with chronic obstructive pulmonary disease identified evidence of benefit from vaccination (*199*).

Immunocompromised Persons

TIV produces adequate antibody concentrations against influenza among vaccinated HIV-infected persons who have no or minimal AIDS-related symptoms (*200–202*). Among persons who have advanced HIV disease and low CD4+ T-lymphocyte cell counts, TIV might not induce protective antibody titers (*202,203*); a second dose of vaccine does not improve the immune response in these persons (*203,204*). A randomized, placebo-controlled trial determined that TIV was highly effective in preventing symptomatic, laboratory-confirmed influenza virus infection among HIV-infected persons with a mean of 400 CD4+ T-lymphocyte cells/mm^3; however, a limited number of persons with CD4+ T-lymphocyte cell counts of <200 were included in that study (*204*). A nonrandomized study of HIV-infected persons determined that influenza vaccination was most effective among persons with >100 CD4+ cells and among those with <30,000 viral copies of HIV type-1/mL (*95*).

On the basis of certain limited studies, immunogenicity for persons with solid organ transplants varies according to transplant type. Among persons with kidney or heart transplants, the proportion who developed seroprotective antibody concentrations was similar or slightly reduced compared with healthy persons (*205–207*). However, a study among persons with liver transplants indicated reduced immunologic responses to influenza vaccination (*208–210*), especially if vaccination occurred within the 4 months after the transplant procedure (*208*).

Pregnant Women and Neonates

Pregnant women have protective levels of anti-influenza antibodies after vaccination (*211,212*). Passive transfer of anti-influenza antibodies that might provide protection from vaccinated women to neonates has been reported (*211,213–216*). One randomized controlled trial conducted in Bangladesh that provided vaccination to pregnant women during the third trimester demonstrated a 29% reduction in respiratory illness with fever among the mothers and a 36% reduction in respiratory illness with fever among their infants during the first 6 months of life. In addition, infants born to vaccinated women had a 63% reduction in laboratory-confirmed influenza illness during the first 6 months of life (*217*). All women in this trial breastfed their infants (mean duration: 14 weeks). However, a retrospective study conducted during 1997–2002 that used clinical records data did not indicate a reduction in ILI among vaccinated pregnant women or their infants (*218*). In another study conducted during 1995–2001, medical visits for respiratory illness among infants were not reduced substantially (*219*).

Adults Aged ≥65 Years

One prospective cohort study indicated that immunogenicity among hospitalized persons who either were aged ≥65 years or were aged 18–64 years and had one or more chronic medical conditions was similar compared with outpatients (*220*). Immunogenicity data from three studies among persons aged ≥65 years indicate that higher-dose preparations elicit substantially higher hemagglutinin inhibition (HI) titers compared with the standard dose (*221–223*). In one study, prespecified criteria for superiority (defined as when the lower bound of the two-sided confidence interval of a ratio of geometric mean HI titers is >1.5 and the difference in fourfold rise of HI titers is >10%) were demonstrated for influenza A (H1N1) and influenza A (H3N2) antigens among persons aged ≥65 years who received a TIV formulation (Fluzone High-Dose, sanofi pasteur) that contains four times the standard amount of HA antigen (180 mcg [60 mcg of each strain]) of influenza virus hemagglutinin per dose (*222,224*). Prespecified criteria for noninferiority to a standard-dose vaccine (Fluzone, sanofi pasteur) was demonstrated for the influenza B antigen (*222*).

The only randomized controlled trial among community-dwelling persons aged ≥60 years reported a vaccine efficacy of 58% (95% CI = 26%–77%) against laboratory-confirmed influenza illness during a season when the vaccine strains were considered to be well-matched to circulating strains (*225*). Additional information from this trial published separately indicated that efficacy among those aged ≥70 years was 57% (95% CI = -36%–87%), similar to younger persons. However, few persons aged >75 years participated in this study, and the wide confidence interval for the estimate of efficacy among participants aged ≥70 years could not exclude no effect (i.e., included 0) (*226*). Influenza vaccine effectiveness in preventing MAARI among the elderly in nursing homes has been estimated at 20%–40% (*227,228*), and reported outbreaks among well-vaccinated nursing home populations have suggested that vaccination might not have any significant effectiveness when circulating strains are drifted from vaccine strains (*229,230*). In contrast, some studies have indicated that vaccination can be up-to-80% effective in preventing influenza-related death (*227,231–233*). Among elderly persons not living in nursing homes or similar long-term–care facilities, influenza vaccine is 27%–70% effective in preventing hospitalization for pneumonia and influenza (*234–236*). Influenza vaccination reduces the frequency of secondary complications and reduces the risk for influenza-related hospitalization and death among community-dwelling adults aged ≥65 years with and without high-risk medical conditions (e.g., heart disease and diabetes) (*235–240*). However, studies demonstrating large reductions in hospitalizations and deaths among the vaccinated elderly have been conducted using medical record databases and have not measured reductions in laboratory-confirmed influenza illness. These studies have been challenged because of concerns that they have not controlled adequately for differences in the propensity for healthier persons to be more likely than less healthy persons to receive vaccination (*134,135,232,241–244*).

Immunogenicity of Inactivated 2009 Pandemic H1N1 Vaccines

The 2010–11 seasonal influenza vaccine will contain an influenza A (H1N1) California/7/2009-like strain, which was also the strain used for the 2009 pandemic H1N1 monovalent vaccines. Clinical studies of the 2009 H1N1 monovalent vaccines indicate that this vaccine antigen is immunogenic and response rates are similar to those observed after immunization with influenza A antigens found in typical seasonal influenza vaccines. Among children aged 6–35 months, 19%–92% responded with an HI titer ≥40 at ≥21 days after 1 dose, and >90% responded with an HI titer ≥40 after 2 doses separated

by ≥21 days (*159,160*; National Institutes of Health, unpublished data, 2010). Among children aged 3 –9 years, 44%–93% responded with an HI titer ≥40 at 21 or more days after 1 dose, and >90% responded with an HI titer ≥40 after 2 doses separated by ≥21 days (*158–160*; National Institutes of Health, unpublished data, 2010). Among older children and adults, response rates after 1 dose exceeded 90% (*160,184*) although geometric mean titers were substantially lower among adults aged ≥50 years in one study (*184*) and among adults aged ≥65 years (*160*). Additional data on 2009 H1N1 pandemic vaccine immunogenicity among persons with chronic medical conditions or pregnant women are not yet available, but results from studies in other groups suggest that immunogenicity is likely to be similar to that observed in studies of seasonal vaccine immunogenicity.

TIV Dosage, Administration, and Storage

The composition of TIV varies according to manufacturer, and package inserts should be consulted. TIV formulations in multidose vials contain the vaccine preservative thimerosal; preservative-free, single-dose preparations also are available. TIV should be stored at 35°F–46°F (2°C–8°C) and should not be frozen. TIV that has been frozen should be discarded. Dosage recommendations and schedules vary according to age group (Table 2). Vaccine prepared for a previous influenza season should not be administered to provide protection for any subsequent season.

The intramuscular route is recommended for TIV. Adults and older children should be vaccinated in the deltoid muscle. A needle length of ≥1 inch (≥25 mm) should be considered for persons in these age groups because needles of <1 inch might be of insufficient length to penetrate muscle tissue in certain adults and older children (*245*). When injecting into the deltoid muscle among children with adequate deltoid muscle mass, a needle length of ⅞–1¼ inches is recommended (*245*).

Infants and young children should be vaccinated in the anterolateral aspect of the thigh. A needle length of ⅞–1 inch should be used for children aged <12 months.

Adverse Events After Receipt of TIV

Children

Studies support the safety of annual TIV in children and adolescents. The largest published postlicensure population-based study assessed TIV safety in 251,600 children aged <18 years (including 8,476 vaccinations in children aged 6–23 months) who were enrolled in one of five health maintenance organizations within the Vaccine Safety Datalink (VSD) during 1993–1999. This study indicated no increase in clinically important medically attended events during the 2 weeks after inactivated influenza vaccination compared with control periods 3–4 weeks before and after vaccination (*246*). A retrospective cohort study using VSD medical records data from 45,356 children aged 6–23 months during 1991–2003 provided additional evidence supporting overall safety of TIV in this age group. During the 2 weeks after vaccination, TIV was not associated with statistically significant increases in any clinically important medically attended events other than gastritis/duodenitis, compared with 2-week control time periods before and after vaccination. Analysis also indicated that 13 diagnoses, including acute upper respiratory illness, otitis media, and asthma, were substantially less common during the 2 weeks after influenza vaccine. On chart review, most children with a diagnosis of gastritis/duodenitis had acute episodes of vomiting or diarrhea, which usually are self-limiting symptoms. The positive or negative associations between TIV and any of these diagnoses do not necessarily indicate a causal relationship (*247*). The study identified no increased risk for febrile seizure during the 3 days after vaccination. Similarly, no increased risk for febrile seizure was observed during the 14 days after TIV vaccination, after controlling for simultaneous receipt of measles-mumps-rubella (MMR) vaccine which has a known association with febrile seizures in the second week after MMR vaccination (*247*). Another analysis assessed risk for prespecified adverse events in the VSD, including seizures and Guillan-Barré Syndrome (GBS), after TIV during three influenza seasons (2005–06, 2006–07, and 2007–08). No elevated risk for adverse events was identified among 1,195,552 TIV doses administered to children aged <18 years (*248*).

In a study of 791 healthy children aged 1–15 years, postvaccination fever was noted among 12% of those aged 1–5 years, 5% among those aged 6–10 years, and 5% among those aged 11–15 years (*139*). Fever, malaise, myalgia, and other systemic symptoms that can occur after vaccination with inactivated vaccine most often affect persons who have had no previous exposure to the influenza virus antigens in the vaccine (e.g., young children) (*249*). These reactions begin 6–12 hours after vaccination and can persist for 1–2 days (*249*).

Data about potential adverse events among children after influenza vaccination are available from the Vaccine Adverse Event Reporting System (VAERS). Because of the limitations of passive reporting systems, determining causality for specific types of adverse events usually is not possible using VAERS data alone. Published reviews of VAERS reports submitted after administration of TIV to children aged 6–23 months indicated that the most frequently reported adverse events were fever, rash, injection-site reactions, and seizures; the majority of the limited number of reported seizures appeared

TABLE 2. Influenza vaccines for different age groups — United States, 2010–11 season*

Vaccine	Trade name	Manufacturer	Presentation	Mercury content (mcg Hg/0.5 mL dose)	Age group	No. of doses	Route
TIV†	Fluzone	sanofi pasteur	0.25 mL prefilled syringe	0.0	6–35 mos	1 or 2§	Intramuscular¶
			0.5 mL prefilled syringe	0.0	≥36 mos	1 or 2§	Intramuscular
			0.5 mL vial	0.0	≥36 mos	1 or 2§	Intramuscular
			5.0 mL multidose vial	25.0	≥6 mos	1 or 2§	Intramuscular
TIV	Fluvirin	Novartis Vaccine	5.0 mL multidose vial	24.5	≥4 yrs	1 or 2§	Intramuscular
			0.5 mL prefilled syringe	<1.0			
TIV	Fluarix	Glaxo SmithKline	0.5 mL prefilled syringe	0.0	≥3 yrs	1	Intramuscular
TIV	FluLaval	Glaxo SmithKline	5.0 mL multidose vial	25.0	≥18 yrs	1	Intramuscular
TIV	Afluria	CSL Biotherapies	0.5 mL prefilled syringe	0.0	≥6 mos	1	Intramuscular
			5.0 mL multidose vial	25.0			
TIV High Dose**	Fluzone High-Dose	sanofi pasteur	0.5 mL prefilled syringe	0.0	≥65 yrs	1	Intramuscular
LAIV††	FluMist§§	MedImmune	0.2 mL sprayer, divided dose	0.0	2–49 yrs	1 or 2§	Intranasal

* Immunization providers should check Food and Drug Administration–approved prescribing information for 2010–11 influenza vaccines for the most updated information.

† Trivalent inactivated vaccine.

§ Children aged 6 months–8 years who have never received a seasonal TIV before or who did not receive at least 1 dose of an influenza A (H1N1) 2009 monovalent vaccine should receive 2 doses, spaced ≥4 weeks apart. Those children aged 6 months–8 years who were vaccinated for the first time in the 2009–10 season with the seasonal 2009–10 seasonal vaccine but who received only 1 dose should receive 2 doses of the 2010–11 influenza vaccine formula, spaced ≥4 weeks apart.

¶ For adults and older children, the recommended site of vaccination is the deltoid muscle. The preferred site for infants and young children is the anterolateral aspect of the thigh.

** Trivalent inactivated vaccine high dose. A 0.5-mL dose contains 60 mcg each of A/California/7/2009 (H1N1)-like, A/Perth/16/2009 (H3N2)-like, and B/Brisbane/60/2008-like antigens.

†† Live attenuated influenza vaccine.

§§ FluMist is shipped refrigerated and stored in the refrigerator at 36°F–46°F (2°C–8°C) after arrival in the vaccination clinic. The dose is 0.2 mL divided equally between each nostril. Health-care providers should consult the medical record, when available, to identify children aged 2–4 years with asthma or recurrent wheezing that might indicate asthma. In addition, to identify children who might be at greater risk for asthma and possibly at increased risk for wheezing after receiving LAIV, parents or caregivers of children aged 2–4 years should be asked: "In the past 12 months, has a health-care provider ever told you that your child had wheezing or asthma?" Children whose parents or caregivers answer "yes" to this question and children who have asthma or who had a wheezing episode noted in the medical record within the past 12 months should not receive FluMist.

to be febrile (*250,251*). Seizure and fever were the leading serious adverse events (SAEs) reported to VAERS in these studies (*250,2511*); analysis of VSD data did not confirm an association with febrile seizures and influenza vaccination as observed in VAERS (*247*).

In April 2010, Australia's Therapeutic Goods Administration reported preliminary data indicating an elevated risk for febrile reactions, including febrile seizures, among young children in Australia who received the 2010 trivalent vaccine Fluvax Jr., the southern hemisphere inactivated trivalent vaccine for children manufactured by CSL Biotherapies. The risk for febrile seizures was estimated to be as high as five to nine cases per 1,000 vaccinated children aged <5 years, and most seizures occurred among children aged <3 years. Other influenza vaccines, including previous seasonal and pandemic influenza vaccines manufactured by CSL Biotherapies, have not been associated with an increased risk for febrile seizures among children in the United States or Australia. As of July 2010, no cause for the increased frequency of febrile reactions among young children who received the southern hemisphere CSL Biotherapies vaccine had been identified (*252*). ACIP will continue to monitor safety studies being conducted in Australia and might provide further guidance on use of Afluria, the northern hemisphere trivalent vaccine manufactured by CSL Biotherapies later in 2010. Immunization providers should consult updated information on use of the CSL vaccine from CDC (http://www.cdc.gov/flu) and FDA (http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/VaccineSafety/default.htm).

Adults

In placebo-controlled studies among adults, the most frequent side effect of vaccination was soreness at the vaccination site (affecting 10%–64% of patients) that lasted <2 days (*253,254*). These local reactions typically were mild and rarely interfered with the recipients' ability to conduct usual daily activities. Placebo-controlled trials demonstrated that among older persons and healthy young adults, administration of TIV is not associated with higher rates for systemic symptoms (e.g., fever, malaise, myalgia, and headache) when compared with

Please note: An erratum has been published for this issue. To view the erratum, please click here.

placebo injections (*77,198,253–255*). One prospective cohort study indicated that the rate of adverse events was similar among hospitalized persons who either were aged ≥65 years or were aged 18–64 years and had one or more chronic medical conditions compared with outpatients (*220*). Among adults vaccinated in consecutive years, reaction frequencies declined in the second year of vaccination (*256*). In clinical trials, SAEs were reported to occur after vaccination with TIV at a rate of <1%. Adverse events in adults aged ≥18 years reported to VAERS during 1990–2005 were analyzed. The most common adverse events reported to VAERS in adults included injection-site reactions, pain, fever, myalgia, and headache. The VAERS review identified no new safety concerns. Fourteen percent of the TIV VAERS reports in adults were classified as SAEs, similar to proportions seen overall in VAERS. The most common SAE reported after receipt of TIV in VAERS in adults was GBS (*257*). The potential association between TIV and GBS has been an area of ongoing research (see Guillain-Barré Syndrome and TIV). No elevated risk for prespecified events after TIV was identified among 4,773,956 adults in a VSD analysis (*249*).

Solicited injection-site reactions and systemic adverse events among persons aged ≥65 years were more frequent after vaccination with a vaccine containing 180 mcg of HA antigen (Fluzone High-Dose, sanofi pasteur) compared with a standard dose (45 mcg) (Fluzone, Sanofi pasteur vaccines) but were typically mild and transient. In the largest study, 915 (36%) of 2,572 persons who received Fluzone High-Dose reported injection-site pain, compared with 306 (24%) of the 1,260 subjects who received Fluzone. The pain was of mild intensity and resolved within 3 days in the majority of subjects. Among Fluzone High Dose recipients, 1.1% reported moderate to severe fever; this was substantially higher than the 0.3% of Fluzone recipients who reported this systemic adverse event (*222*). During the 6-month follow-up period, SAEs were reported in 6% of the High-Dose recipients and 7% of the Fluzone recipients (*222*).

Pregnant Women and Neonates

FDA has classified TIV as a "Pregnancy Category C" medication, indicating that adequate animal reproduction studies have not been conducted. Available data do not indicate that influenza vaccine causes fetal harm when administered to a pregnant woman. One study of approximately 2,000 pregnant women who received TIV during pregnancy demonstrated no adverse fetal effects and no adverse effects during infancy or early childhood (*258*). A matched case-control study of 252 pregnant women who received TIV within the 6 months before delivery determined no adverse events after vaccination among pregnant women and no difference in pregnancy outcomes compared with 826 pregnant women who were not vaccinated (*212*). During 2000–2003, an estimated 2 million pregnant women were vaccinated, and only 20 adverse events among women who received TIV were reported to VAERS during this time, including nine injection-site reactions and eight systemic reactions (e.g., fever, headache, and myalgias). In addition, three miscarriages were reported, but these were not known to be related causally to vaccination (*259*). Similar results have been reported in certain smaller studies (*211,213,260*), and a recent international review of data on the safety of TIV concluded that no evidence exists to suggest harm to the fetus (*261*). The rate of adverse events associated with TIV was similar to the rate of adverse events among pregnant women who received pneumococcal polysaccharide vaccine in one small randomized controlled trial in Bangladesh, and no severe adverse events were reported in any study group (*217*).

Persons with Chronic Medical Conditions

In a randomized cross-over study of children and adults with asthma, no increase in asthma exacerbations was reported for either age group (*262*), and two additional studies also have indicated no increase in wheezing among vaccinated asthmatic children (*177*) or adults (*195*). One study reported that 20%–28% of children aged 9 months–18 years with asthma had injection-site pain and swelling at the site of influenza vaccination (*167*), and another study reported that 23% of children aged 6 months–4 years with chronic heart or lung disease had injection-site reactions (*153*). A blinded, randomized, cross-over study of 1,952 adults and children with asthma demonstrated that only self-reported "body aches" were reported more frequently after receipt of TIV (25%) than placebo-injection (21%) (*262*). However, a placebo-controlled trial of TIV indicated no difference in injection-site reactions among 53 children aged 6 months–6 years with high-risk medical conditions or among 305 healthy children aged 3–12 years (*157*).

Among children with high-risk medical conditions, one study of 52 children aged 6 months–3 years reported fever among 27% and irritability and insomnia among 25% (*153*), and a study among 33 children aged 6–18 months reported that one child had irritability and one had a fever and seizure after vaccination (*263*). No placebo comparison group was used in these studies.

Immunocompromised Persons

Data demonstrating safety of TIV for HIV-infected persons are limited, but no evidence exists that vaccination has a clinically important impact on HIV infection or immunocompetence. One study demonstrated a transient (i.e., 2–4 week) increase in HIV RNA (ribonucleic acid) levels in one

HIV-infected person after influenza virus infection (*264*). Studies have demonstrated a transient increase in replication of HIV-1 in the plasma or peripheral blood mononuclear cells of HIV-infected persons after vaccine administration (*202,265*). However, more recent and better-designed studies have not documented a substantial increase in the replication of HIV (*266–269*). CD4+ T-lymphocyte cell counts or progression of HIV disease have not been reduced after influenza vaccination among HIV-infected persons compared with unvaccinated HIV-infected persons (*202,270*). Limited information is available about the effect of antiretroviral therapy on increases in HIV RNA levels after either natural influenza virus infection or influenza vaccination (*94,271*).

Data are similarly limited for persons with other immunocompromising conditions. In small studies, vaccination did not affect allograft function or cause rejection episodes in recipients of kidney transplants (*205,206*), heart transplants (*207*), or liver transplants (*208*).

Immediate Hypersensitivity Reactions After Receipt of Influenza Vaccines

Vaccine components rarely can cause allergic reactions, also called immediate hypersensitivity reactions, among certain recipients. Immediate hypersensitivity reactions are mediated by preformed immunoglobulin E (IgE) antibodies against a vaccine component and usually occur within minutes to hours of exposure (*272*). Symptoms of immediate hypersensitivity range from mild urticaria (hives) and angioedema to anaphylaxis. Anaphylaxis is a severe life-threatening reaction that involves multiple organ systems and can progress rapidly. Symptoms and signs of anaphylaxis can include but are not limited to generalized urticaria, wheezing, swelling of the mouth and throat, difficulty breathing, vomiting, hypotension, decreased level of consciousness, and shock. Minor symptoms such as red eyes or hoarse voice also might be present *(246,272–275)*.

Allergic reactions might be caused by the vaccine antigen, residual animal protein, antimicrobial agents, preservatives, stabilizers, or other vaccine components (*276*). Manufacturers use a variety of compounds to inactivate influenza viruses and add antibiotics to prevent bacterial growth. Package inserts for specific vaccines of interest should be consulted for additional information. ACIP has recommended that all vaccine providers should be familiar with the office emergency plan and be certified in cardiopulmonary resuscitation (*246*). The Clinical Immunization Safety Assessment (95% CISA) network, a collaboration between CDC and six medical research centers with expertise in vaccination safety, has developed an algorithm to guide evaluation and revaccination decisions for persons with suspected immediate hypersensitivity after vaccination (*272*).

Immediate hypersensitivity reaction after receipt of TIV and LAIV are rare. A VSD study of children aged <18 years in four health maintenance organizations during 1991–1997 estimated the overall risk for postvaccination anaphylaxis after childhood vaccine to be approximately 1.5 cases per 1 million doses administered, and in this study, no cases were identified in TIV recipients (*277*). Anaphylaxis occurring after receipt of TIV and LAIV in adults has been reported rarely to VAERS (*257*).

Some immediate hypersensitivity reactions after receipt of TIV or LAIV are caused by the presence of residual egg protein in the vaccines (*278*). Although influenza vaccines contain only a limited quantity of egg protein, this protein can induce immediate hypersensitivity reactions among persons who have severe egg allergy. Asking persons if they can eat eggs without adverse effects is a reasonable way to determine who might be at risk for allergic reactions from receiving influenza vaccines (*246*). Persons who have had symptoms such as hives or swelling of the lips or tongue or who have experienced acute respiratory distress after eating eggs should consult a physician for appropriate evaluation to help determine if future influenza vaccine should be administered. Persons who have documented IgE-mediated hypersensitivity to eggs, including those who have had occupational asthma related to egg exposure or other allergic responses to egg protein, also might be at increased risk for allergic reactions to influenza vaccine, and consultation with a physician before vaccination should be considered (*279–281*). A regimen has been developed for administering influenza vaccine to asthmatic children with severe disease and egg hypersensitivity (*280*).

Hypersensitivity reactions to other vaccine components also can occur rarely. Although exposure to vaccines containing thimerosal can lead to delayed-type (Type IV) hypersensitivity (*282*), the majority of patients do not have reactions to thimerosal when it is administered as a component of vaccines, even when patch or intradermal tests for thimerosal indicate hypersensitivity (*283,284*). When reported, hypersensitivity to thimerosal typically has consisted of local delayed hypersensitivity reactions (*283*).

Ocular and Respiratory Symptoms After Receipt of TIV

Ocular or respiratory symptoms have been reported occasionally within 24 hours after TIV administration, but these symptoms typically are mild and resolve quickly without specific treatment. In some trials conducted in the United States,

ocular or respiratory symptoms included red eyes (<1%–6%), cough (1%–7%), wheezing (1%), and chest tightness (1%–3%) (*274,275,285–287*). However, most of these trials were not placebo-controlled, and causality cannot be determined. In addition, ocular and respiratory symptoms are features of a variety of respiratory illnesses and seasonal allergies that would be expected to occur coincidentally among vaccine recipients unrelated to vaccination. A placebo-controlled vaccine effectiveness study among young adults indicated that 2% of persons who received the 2006–07 formulation of Fluzone (sanofi pasteur) reported red eyes compared with none of the controls (p=0.03) (*288*). A similar trial conducted during the 2005–06 influenza season indicated that 3% of Fluzone recipients reported red eyes compared with 1% of placebo recipients; however the difference was not statistically significant (*289*).

Oculorespiratory syndrome (ORS), an acute, self-limited reaction to TIV with prominent ocular and respiratory symptoms, was first described during the 2000–01 influenza season in Canada. The initial case-definition for ORS was the onset of one or more of the following within 2–24 hours after receiving TIV: bilateral red eyes and/or facial edema and/or respiratory symptoms (coughing, wheezing, chest tightness, difficulty breathing, sore throat, hoarseness or difficulty swallowing, cough, wheeze, chest tightness, difficulty breathing, sore throat, or facial swelling) (*290*). ORS was first described in Canada and strongly associated with one vaccine preparation (Fluviral S/F, Shire Biologics, Quebec, Canada) not available in the United States during the 2000–01 influenza season (*291*). Subsequent investigations identified persons with ocular or respiratory symptoms meeting an ORS case-definition in safety monitoring systems and trials that had been conducted before 2000 in Canada, the United States, and several European countries (*292–294*).

The cause of ORS has not been established; however, studies suggest that the reaction is not IgE-mediated (*295*). After changes in the manufacturing process of the vaccine preparation associated with ORS during 2000–01, the incidence of ORS in Canada was reduced greatly (*293*). In one placebo-controlled study, only hoarseness, cough, and itchy or sore eyes (but not red eyes) were strongly associated with a reformulated Fluviral preparation. These findings indicated that ORS symptoms following use of the reformulated vaccine were mild, resolved within 24 hours, and might not typically be of sufficient concern to cause vaccine recipients to seek medical care (*296*).

Ocular and respiratory symptoms reported after TIV administration, including ORS, have some similarities with immediate hypersensitivity reactions. One study indicated that the risk for ORS recurrence with subsequent vaccination is low, and persons with ocular or respiratory symptoms (e.g., bilateral red eyes, cough, sore throat, or hoarseness) after receipt of TIV that did not involve the lower respiratory tract have been revaccinated without reports of SAEs after subsequent exposure to TIV (*297*).

Revaccination in Persons Who Experienced Ocular or Respiratory Symptoms After Receipt of TIV

When assessing whether a patient who experienced ocular and respiratory symptoms should be revaccinated, providers should determine if concerning signs and symptoms of Ig-E mediated immediate hypersensitivity are present (see Immediate Hypersensitivity after Influenza Vaccines). Healthcare providers who are unsure whether symptoms reported or observed after receipt of TIV represent an IgE-mediated hypersensitivity immune response should seek advice from an allergist/immunologist. Persons with symptoms of possible IgE-mediated hypersensitivity after receipt of TIV should not receive influenza vaccination unless hypersensitivity is ruled out or revaccination is administered under close medical supervision (*272*).

Ocular or respiratory symptoms observed after receipt of TIV often are coincidental and unrelated to TIV administration, as observed among placebo recipients in some randomized controlled studies. Determining whether ocular or respiratory symptoms are coincidental or related to possible ORS might not be possible. Persons who have had red eyes, mild upper facial swelling, or mild respiratory symptoms (e.g., sore throat, cough, or hoarseness) after receipt of TIV without other concerning signs or symptoms of hypersensitivity can receive TIV in subsequent seasons without further evaluation. Two studies indicated that persons who had symptoms of ORS after receipt of TIV were at a higher risk for ORS after subsequent TIV administration; however, these events usually were milder than the first episode (*297,298*).

Contraindications and Precautions for Use of TIV

TIV is contraindicated and should not be administered to persons known to have anaphylactic hypersensitivity to eggs or to other components of the influenza vaccine unless the recipient has been desensitized. Prophylactic use of antiviral agents is an option for preventing influenza among such persons. Information about vaccine components is located in package inserts from each manufacturer. Persons with moderate to severe acute febrile illness usually should not be vaccinated until their symptoms have abated. Moderate or severe acute illness with or without fever is a precaution for TIV. GBS within 6

weeks following a previous dose of influenza vaccine is considered to be a precaution for use of influenza vaccines.

Guillain-Barré Syndrome and TIV

The annual incidence of GBS is 10–20 cases per 1 million adults (*299*). Substantial evidence exists that multiple infectious illnesses, most notably *Campylobacter jejuni* gastrointestinal infections and upper respiratory tract infections, are associated with GBS (*300–302*). A recent study identified serologically confirmed influenza virus infection as a trigger of GBS, with time from onset of influenza illness to GBS of 3–30 days. The estimated frequency of influenza-related GBS was four to seven times higher than the frequency that has been estimated for influenza-vaccine–associated GBS (*303*).

The 1976 swine influenza vaccine was associated with an increased frequency of GBS, estimated at one additional case of GBS per 100,000 persons vaccinated (*304,305*). The risk for influenza-vaccine–associated GBS was higher among persons aged ≥25 years than among persons aged <25 years (*306*). However, obtaining epidemiologic evidence for a small increase in risk for a rare condition with multiple causes is difficult, and no evidence consistently exists for a causal relation between subsequent vaccines prepared from other influenza viruses and GBS.

None of the studies conducted using influenza vaccines other than the 1976 swine influenza vaccine has demonstrated an increase in GBS associated with influenza vaccines on the order of magnitude seen in 1976–77. During three of four influenza seasons studied during 1977–1991, the overall relative risk estimates for GBS after influenza vaccination were not statistically significant in any of these studies (*307–309*). However, in a study of the 1992–93 and 1993–94 seasons, the overall relative risk for GBS was 1.7 (95% CI = 1.0–2.8; p=0.04) during the 6 weeks after vaccination, representing approximately one additional case of GBS per 1 million persons vaccinated; the combined number of GBS cases peaked 2 weeks after vaccination (*305*). Results of a study that examined health-care data from Ontario, Canada, during 1992–2004 demonstrated a small but statistically significant temporal association between receiving influenza vaccination and subsequent hospital admission for GBS. However, no increase in cases of GBS at the population level was reported after introduction of a mass public influenza vaccination program in Ontario beginning in 2000 (*310*). Data from VAERS have documented decreased reporting of GBS occurring after vaccination across age groups over time, despite overall increased reporting of other non-GBS conditions occurring after administration of influenza vaccine (*304*). Published data from the United Kingdom's General Practice Research Database (GPRD) indicated that influenza vaccine was associated with a decreased risk for GBS, although whether this was associated with protection against influenza or confounding because of a "healthy vaccinee" effect (e.g., healthier persons might be more likely to be vaccinated and also be at lower risk for GBS) (*311*) is unclear. A separate GPRD analysis identified no association between vaccination and GBS for a 9-year period; only three cases of GBS occurred within 6 weeks after administration of influenza vaccine (*312*). A third GPRD analysis indicated that GBS was associated with recent ILI, but not influenza vaccination (*313,314*).

The estimated risk for GBS (on the basis of the few studies that have demonstrated an association between vaccination and GBS) is low (i.e., approximately one additional case per 1 million persons vaccinated). The potential benefits of influenza vaccination in preventing serious illness, hospitalization, and death substantially outweigh these estimates of risk for vaccine-associated GBS. No evidence indicates that the case-fatality ratio for GBS differs among vaccinated persons and those not vaccinated. Preliminary data from the systems monitoring influenza A (H1N1) 2009 monovalent vaccines suggest that if a risk exists for GBS after receiving inactivated vaccines, it is not substantially higher than that reported in some seasons for TIV (*315*); analyses are ongoing to quantify any potential GBS risk (*316*).

Use of TIV Among Patients with a History of GBS

The incidence of GBS among the general population is low, but persons with a history of GBS have a substantially greater likelihood of subsequently experiencing GBS than persons without such a history (*299*). Thus, the likelihood of coincidentally experiencing GBS after influenza vaccination is expected to be greater among persons with a history of GBS than among persons with no history of this syndrome. Whether influenza vaccination specifically might increase the risk for recurrence of GBS is unknown. Among 311 patients with GBS who responded to a survey, 11 (4%) reported some worsening of symptoms after influenza vaccination; however, some of these patients had received other vaccines at the same time, and recurring symptoms were generally mild (*317*). However, as a precaution, persons who are not at high risk for severe influenza complications and who are known to have experienced GBS within 6 weeks of receipt of an influenza vaccine generally should not be vaccinated. As an alternative, physicians might consider using influenza antiviral chemoprophylaxis for these persons. Although data are limited, the established benefits of influenza vaccination might outweigh the risks for many persons who have a history of GBS and who also are at high risk for severe complications from influenza.

Vaccine Preservative (Thimerosal) in Multidose Vials of TIV

Thimerosal, a mercury-containing antibacterial compound, has been used as a preservative in vaccines and other medications since the 1930s (*318*) and is used in multidose vial preparations of TIV to reduce the likelihood of bacterial growth. No scientific evidence indicates that thimerosal in vaccines, including influenza vaccines, is a cause of adverse events other than occasional local hypersensitivity reactions in vaccine recipients. In addition, no scientific evidence indicates that thimerosal-containing vaccines are a cause of adverse events among children born to women who received vaccine during pregnancy. The weight of accumulating evidence does not suggest an increased risk for neurodevelopment disorders from exposure to thimerosal-containing vaccines (*319–328*). The U.S. Public Health Service and other organizations have recommended that efforts be made to eliminate or reduce the thimerosal content in vaccines as part of a strategy to reduce mercury exposures from all sources (*319,320,329*). Also, continuing public concerns about exposure to mercury in vaccines has been viewed as a potential barrier to achieving higher vaccine coverage levels and reducing the burden of vaccine-preventable diseases, including influenza. Since mid-2001, vaccines routinely recommended for infants aged <6 months in the United States have been manufactured either without or with greatly reduced (trace) amounts of thimerosal. As a result, a substantial reduction in the total mercury exposure from vaccines for infants and children already has been achieved (*246*). ACIP and other federal agencies and professional medical organizations continue to support efforts to provide thimerosal-preservative–free vaccine options.

The U.S. vaccine supply for infants and pregnant women is in a period of transition as manufacturers expand the availability of thimerosal-reduced or thimerosal-free vaccine to reduce the cumulative exposure of infants to mercury. Other environmental sources of mercury exposure are more difficult or impossible to avoid or eliminate (*319*). The benefits of influenza vaccination for all recommended groups, including pregnant women and young children, outweigh concerns on the basis of a theoretic risk from thimerosal exposure through vaccination. The risks for severe illness from influenza virus infection are elevated among both young children and pregnant women, and vaccination has been demonstrated to reduce the risk for severe influenza illness and subsequent medical complications. In contrast, no harm from exposure to vaccine containing thimerosal preservative has been demonstrated. For these reasons, persons recommended to receive TIV may receive any age- and risk factor–appropriate vaccine preparation, depending on availability. An analysis of VAERS reports identified no difference in the safety profile of preservative-containing compared with preservative-free TIV vaccines in infants aged 6–23 months (*251*).

Nonetheless, some states have enacted legislation banning the administration of vaccines containing mercury; the provisions defining mercury content vary (*330*). LAIV and many of the single-dose vial or syringe preparations of TIV are thimerosal-free, and the number of influenza vaccine doses that do not contain thimerosal as a preservative is expected to increase (Table 2). However, these laws might present a barrier to vaccination unless influenza vaccines that do not contain thimerosal as a preservative are routinely available in those states.

Dosage, Administration, and Storage of LAIV

Each dose of LAIV contains the same three vaccine antigens used in TIV. However, the antigens are constituted as live, attenuated, cold-adapted, temperature-sensitive vaccine viruses. Providers should refer to the package insert, which contains additional information about the formulation of this vaccine and other vaccine components. LAIV does not contain thimerosal. LAIV is made from attenuated viruses that are able to replicate efficiently only at temperatures present in the nasal mucosa. LAIV recipients might experience nasal congestion or mild fever, which is probably a result of effects of intranasal vaccine administration or local viral replication. However, LAIV does not typically cause the more prominent systemic symptoms of influenza such as high fever, myalgia, and severe fatigue (*331*).

LAIV is intended for intranasal administration only and should not be administered by the intramuscular, intradermal, or intravenous route. LAIV is not licensed for vaccination of children aged <2 years or adults aged >49 years. LAIV is supplied in a prefilled, single-use sprayer containing 0.2 mL of vaccine. Approximately 0.1 mL (i.e., half of the total sprayer contents) is sprayed into the first nostril while the recipient is in the upright position. An attached dose-divider clip is removed from the sprayer to administer the second half of the dose into the other nostril. LAIV is shipped at 35°F–46°F (2°C–8°C). LAIV should be stored at 35°F–46°F (2°C–8°C) on receipt and can remain at that temperature until the expiration date is reached (*331*). Vaccine prepared for a previous influenza season should not be administered to provide protection for any subsequent season.

Shedding, Transmission, and Stability of LAIV Viruses

Available data indicate that both children and adults vaccinated with LAIV can shed vaccine viruses after vaccination, although in lower amounts than occur typically with shedding of wild-type influenza viruses. In rare instances, shed vaccine viruses can be transmitted from vaccine recipients to unvaccinated persons. However, serious illnesses have not been reported among unvaccinated persons who have been infected inadvertently with vaccine viruses.

One study of 197 children aged 8–36 months in a child care center assessed transmissibility of vaccine viruses from 98 vaccinated children to the other 99 unvaccinated children; 80% of vaccine recipients shed one or more virus strains (mean duration: 7.6 days). One influenza type B vaccine strain isolate was recovered from a placebo recipient and was confirmed to be vaccine-type virus. The type B isolate retained the cold-adapted, temperature-sensitive, attenuated phenotype, and it possessed the same genetic sequence as a virus shed from a vaccine recipient who was in the same play group. The placebo recipient from whom the influenza type B vaccine strain was isolated had symptoms of a mild upper respiratory illness but did not experience any serious clinical events. The estimated probability of acquiring vaccine virus after close contact with a single LAIV recipient in this child care population was 1%–2% (*332*).

Studies assessing whether vaccine viruses are shed have been based on viral cultures or polymerase chain reaction (PCR) detection of vaccine viruses in nasal aspirates from persons who have received LAIV. Among 345 subjects aged 5–49 years, 30% had detectable virus in nasal secretions obtained by nasal swabbing after receiving LAIV. The duration of virus shedding and the amount of virus shed was correlated inversely with age, and maximal shedding occurred within 2 days of vaccination. Symptoms reported after vaccination, including runny nose, headache, and sore throat, did not correlate with virus shedding (*333*). Other smaller studies have reported similar findings (*334,335*). Vaccine strain virus was detected from nasal secretions in one (2%) of 57 HIV-infected adults who received LAIV, none of 54 HIV-negative participants (*336*), and three (13%) of 23 HIV-infected children compared with seven (28%) of 25 children who were not HIV-infected (*337*). No participants in these studies had detectable virus beyond 10 days after receipt of LAIV. The possibility of person-to-person transmission of vaccine viruses was not assessed in these studies (*334–337*).

In clinical trials, viruses isolated from vaccine recipients have retained attenuated phenotypes. In one study, nasal and throat swab specimens were collected from 17 study participants for 2 weeks after vaccine receipt (*338*). Virus isolates were analyzed by multiple genetic techniques. All isolates retained the LAIV genotype after replication in the human host, and all retained the cold-adapted and temperature-sensitive phenotypes. A study conducted in a child care setting demonstrated that limited genetic change occurred in the LAIV strains following replication in the vaccine recipients (*339*).

Immunogenicity, Efficacy, and Effectiveness of LAIV

LAIV virus strains replicate primarily in nasopharyngeal epithelial cells. The protective mechanisms induced by vaccination with LAIV are not understood completely but appear to involve both serum and nasal secretory antibodies. The immunogenicity of the approved LAIV has been assessed in multiple studies conducted among children and adults (*147,340–345*).

Healthy Children

A randomized, double-blind, placebo-controlled trial among 1,602 healthy children aged 15–71 months assessed the efficacy of LAIV against culture-confirmed influenza during two seasons (*346,347*). This trial included a subset of children aged 60–71 months who received 2 doses in the first season. During the first season (1996–97), when vaccine and circulating virus strains were well-matched, efficacy against culture-confirmed influenza was 94% for participants who received 2 doses of LAIV separated by ≥6 weeks, and 89% for those who received 1 dose. During the second season (1997–98), when the A (H3N2) component in the vaccine was not well-matched with circulating virus strains, efficacy (1 dose) was 86%, for an overall efficacy for two influenza seasons of 92%. Receipt of LAIV also resulted in 21% fewer febrile illnesses and a significant decrease in acute otitis media requiring antibiotics (*346,348*). Other randomized, placebo-controlled trials demonstrating the efficacy of LAIV in young children against culture-confirmed influenza include a study conducted among children aged 6–35 months attending child care centers during consecutive influenza seasons (*349*) in which 85%–89% efficacy was observed, and a study conducted among children aged 12–36 months living in Asia during consecutive influenza seasons in which 64%–70% efficacy was documented (*350*). In one community-based, nonrandomized open-label study, reductions in MAARI were observed among children who received 1 dose of LAIV during the 1990–00 and 2000–01 influenza seasons even though antigenically drifted influenza A/H1N1 and B viruses were circulating during that season (*148*). LAIV efficacy in preventing laboratory-confirmed influenza also has been demonstrated in studies comparing the efficacy of LAIV with TIV rather than with a placebo (see Comparisons

of LAIV and TIV Efficacy or Effectiveness). In clinical trials, an increased risk for wheezing postvaccination was observed in LAIV recipients aged <24 months. An increase in hospitalizations also was observed in children aged <24 months after vaccination with LAIV (*331*).

Healthy Adults

A randomized, double-blind, placebo-controlled trial of LAIV effectiveness among 4,561 healthy working adults aged 18–64 years assessed multiple endpoints, including reductions in self-reported respiratory tract illness without laboratory confirmation, work loss, health-care visits, and medication use during influenza outbreak periods. The study was conducted during the 1997–98 influenza season, when the vaccine and circulating A (H3N2) strains were not well-matched. The frequency of febrile illnesses was not substantially decreased among LAIV recipients compared with those who received placebo. However, vaccine recipients had substantially fewer severe febrile illnesses (19% reduction) and febrile upper respiratory tract illnesses (24% reduction), and substantial reductions in days of illness, days of work lost, days with health-care–provider visits, and use of prescription antibiotics and over-the-counter medications (*351,352*). Efficacy against culture-confirmed influenza in a randomized, placebo-controlled study among young adults was 57% in the 2004–05 influenza season, 43% in the 2005–06 influenza season, and 51% in the 2007–08 influenza season, although efficacy in 2004–05 and 2005–06 was not demonstrated to be substantially greater than placebo (*187,288,289*).

Adverse Events After Receipt of LAIV

Healthy Children Aged 2–18 Years

In a subset of healthy children aged 60–71 months from one clinical trial, certain signs and symptoms were reported more often after the first dose among LAIV recipients (n = 214) than among placebo recipients (n = 95), including runny nose (48% and 44%, respectively); headache (18% and 12%, respectively); vomiting (5% and 3%, respectively); and myalgias (6% and 4%, respectively) (*346*). However, these differences were not statistically significant. In other trials, signs and symptoms reported after LAIV administration have included runny nose or nasal congestion (20%–75%), headache (2%–46%), fever (0–26%), vomiting (3%–13%), abdominal pain (2%), and myalgias (0–21%) (*340,342,343,349,353–356*). These symptoms were associated more often with the first dose and were self-limited. A placebo-controlled trial in 9,689 children aged 1–17 years assessed prespecified medically attended outcomes during the 42 days after vaccination (*355*). Following >1,500 statistical analyses in the 42 days after LAIV, elevated risks that were assessed to be biologically plausible were observed for asthma, upper respiratory infection, musculoskeletal pain, otitis media with effusion, and adenitis/adenopathy. The increased risk for wheezing events after LAIV was observed among children aged 18–35 months (RR: 4.06; 90% CI = 1.3–17.9). Of the 16 children with asthma-related events in this study, seven had a history of asthma on the basis of subsequent medical record review. None required hospitalization, and elevated risks for asthma were not observed in other age groups (*355*). In this study, the rate of SAEs was 0.2% in LAIV and placebo recipients; none of the SAEs was judged to be related to the vaccine by the study investigators (*355*).

In a randomized trial, LAIV and TIV were compared among children aged 6–59 months (*357*). Children with medically diagnosed or treated wheezing within 42 days before enrollment or with a history of severe asthma were excluded from this prelicensure study. Among children aged 24–59 months who received LAIV, the rate of medically significant wheezing, using a prespecified definition, was not greater compared with those who received TIV (*357*). Wheezing was observed more frequently among younger LAIV recipients aged 6–23 months in this study; LAIV is not licensed for this age group.

Another study was conducted among >11,000 children aged 18 months–18 years in which 18,780 doses of vaccine were administered over 4 years. For children aged 18 months–4 years, no increase was reported in asthma visits 0–15 days after vaccination compared with the prevaccination period. A significant increase in asthma events was reported 15–42 days after vaccination, but only in vaccine year 1 (*358*). A 4-year, open-label field trial study assessed LAIV safety of >2,000 doses administered to children aged 18 months–18 years with a history of intermittent wheeze who were otherwise healthy. Among these children, no increased risk was reported for medically attended acute respiratory illnesses, including acute asthma exacerbation, during the 0–14 or 0–42 days after LAIV compared with the pre- and postvaccination reference periods (*359*).

Initial data from VAERS during 2007–2008 and 2008–2009, following ACIP's recommendation for use of LAIV in healthy children aged 2–4 years, did not demonstrate an increased frequency of wheezing after administration of LAIV. However, data also indicate that uptake of LAIV among children aged 2–4 years was limited (CDC, unpublished data, 2010). Safety monitoring for wheezing events after LAIV is ongoing.

Adults Aged <50 Years

Among adults, runny nose or nasal congestion (28%–78%), headache (16%–44%), and sore throat (15%–27%) have been reported more often among vaccine recipients than placebo recipients (*346,360*). In one clinical trial among a subset of

healthy adults aged 18–49 years, signs and symptoms reported significantly more often ($p<0.05$) among LAIV recipients (n = 2,548) than placebo recipients (n = 1,290) within 7 days after each dose included cough (14% and 11%, respectively), runny nose (45% and 27%, respectively), sore throat (28% and 17%, respectively), chills (9% and 6%, respectively), and tiredness/weakness (26% and 22%, respectively) (*144*). A review of 460 reports to VAERS after distribution of approximately 2.5 million doses during the 2003–04 and 2004–05 influenza seasons did not indicate any new safety concerns (*361*). Few of the LAIV VAERS reports (9%) were SAEs; respiratory events (47%) were the most common conditions reported (*361*).

The 2010–11 seasonal live attenuated influenza vaccine will contain an influenza A (H1N1) California/7/2009-like strain, which was also the strain used for the 2009 pandemic H1N1 monovalent live attenuated vaccine. (See Safety Monitoring of Pandemic 2009 H1N1 Monovalent Vaccines for additional information about 2009 H1N1 monovalent vaccine safety data among children and adults.)

Persons at Higher Risk for Influenza-Related Complications

Limited data assessing the safety of LAIV use for certain groups at higher risk for influenza-related complications are available. In one study of 54 HIV-infected persons aged 18–58 years with CD4+ counts ≥200 cells/mm^3 who received LAIV, no SAEs were reported during a 1-month follow-up period (*336*). Similarly, one study demonstrated no significant difference in the frequency of adverse events or viral shedding among HIV-infected children aged 1–8 years on effective antiretroviral therapy who were administered LAIV compared with HIV-uninfected children receiving LAIV (*337*). LAIV was well-tolerated among adults aged ≥65 years with chronic medical conditions (*362*). These findings suggest that persons at risk for influenza complications who have inadvertent exposure to LAIV would not have significant adverse events or prolonged viral shedding and that persons who have contact with persons at higher risk for influenza-related complications may receive LAIV.

Safety Monitoring of Pandemic 2009 H1N1 Monovalent Vaccines

The 2010–11 seasonal influenza vaccine will contain an influenza A (H1N1) California/7/2009-like strain, which was also the strain used for the 2009 pandemic H1N1 monovalent vaccines. Clinical immunogenicity and safety studies of the 2009 H1N1 monovalent vaccines indicate that the reactogenicity profile in children and adults is similar to seasonal influenza vaccines (*158–160,184*). Ongoing comprehensive safety monitoring of the pandemic 2009 H1N1 vaccine was implemented as part of the pandemic immunization program (*363*). A nongovernment working group was established by the National Vaccine Advisory Committee to provide an independent review of safety data, with members representing other federal advisory committees as well as experts in internal medicine, pediatrics, immunology, and vaccine safety (*314*). Data from the first 2 months of implementation of H1N1 vaccination from VAERS and VSD suggested a similar safety profile for influenza A (H1N1) 2009 monovalent vaccines and seasonal influenza vaccines. As of July 2010, analysis and review of vaccine safety data from numerous systems were underway (*314,316*).

Comparisons of LAIV and TIV Efficacy or Effectiveness

Both TIV and LAIV have been demonstrated to be effective in children and adults. However, data directly comparing the efficacy or effectiveness of these two types of influenza vaccines are limited and insufficient to identify whether one vaccine might offer a clear advantage over the other in certain settings or populations. Studies comparing the efficacy of TIV to that of LAIV have been conducted in a variety of settings and populations using several different outcomes. One randomized, double-blind, placebo-controlled challenge study that was conducted among 92 healthy adults aged 18–41 years assessed the efficacy of both LAIV and TIV in preventing influenza infection when challenged with wild-type strains that were antigenically similar to vaccine strains (*364*). The overall efficacy in preventing laboratory-documented influenza from all three influenza strains combined was 85% and 71%, respectively, when challenged 28 days after vaccination by viruses to which study participants were susceptible before vaccination. The difference in efficacy between the two vaccines was not statistically significant in this limited study. No additional challenges were conducted to assess efficacy at time points later than 28 days (*364*). In a randomized, double-blind, placebo-controlled trial that was conducted among young adults during the 2004–05 influenza season, when the majority of circulating H3N2 viruses were antigenically drifted from that season's vaccine viruses, the efficacy of LAIV and TIV against culture-confirmed influenza was 57% and 77%, respectively. The difference in efficacy was not statistically significant and was attributable primarily to a difference in efficacy against influenza B (*289*). Similar studies conducted during the 2005–06 and 2007–08 influenza seasons identified no significant difference in vaccine efficacy in 2005–06 (*288*), but a 50% relative efficacy or TIV compared with LAIV in the 2007–08 season (*187*).

A randomized controlled clinical trial conducted among children aged 6–59 months during the 2004–05 influenza season demonstrated a 55% reduction in cases of culture-confirmed influenza among children who received LAIV compared with those who received TIV (*357*). In this study, LAIV efficacy was higher compared with TIV against antigenically drifted viruses and well-matched viruses (*357*). An open-label, nonrandomized, community-based influenza vaccine trial conducted during an influenza season when circulating H3N2 strains were poorly matched with strains contained in the vaccine also indicated that LAIV, but not TIV, was effective against antigenically drifted H3N2 strains during that influenza season. In this study, children aged 5–18 years who received LAIV had significant protection against laboratory-confirmed influenza (37%) and pneumonia and influenza events (50%) (*365*). An observational study conducted among military personnel aged 17–49 years over three influenza seasons indicated that persons who received TIV had a substantially lower incidence of health-care encounters resulting in diagnostic coding for pneumonia and influenza compared with those who received LAIV. However, among new recruits being vaccinated for the first time, the incidence of pneumonia- and influenza-coded health-care encounters among those received LAIV was similar to those receiving TIV (*366*).

Although LAIV is not licensed for use in persons with risk factors for influenza complications, certain studies have compared the efficacy of LAIV to TIV in these groups. LAIV provided 32% increased protection in preventing culture-confirmed influenza compared with TIV in one study conducted among children aged ≥6 years and adolescents with asthma (*367*) and 52% increased protection compared with TIV among children aged 6–71 months with recurrent respiratory tract infections (*368*).

Effectiveness of Vaccination for Decreasing Transmission to Contacts

Decreasing transmission of influenza from caregivers and household contacts to persons at high risk might reduce ILI and complications among persons at high risk. Influenza virus infection and ILI are common among HCP (*369–371*). Influenza outbreaks have been attributed to low vaccination rates among HCP in hospitals and long-term–care facilities (*372–374*). One serosurvey demonstrated that 23% of HCP had serologic evidence of influenza virus infection during a single influenza season; the majority had mild illness or subclinical infection (*369*). Observational studies have demonstrated that vaccination of HCP is associated with decreased deaths among nursing home patients (*375,376*). In one cluster-randomized controlled trial that included 2,604 residents of 44 nursing homes, significant decreases in mortality, ILI, and medical visits for ILI care were demonstrated among residents in nursing homes in which staff were offered influenza vaccination (coverage rate: 48%) compared with nursing homes in which staff were not provided with vaccination (coverage rate: 6%) (*377*). Another trial demonstrated substantially lower rates of ILI among residents and staff absences in nursing homes where staff were specifically targeted for vaccination (coverage rate: 70%) compared with nursing homes where no intervention was attempted (coverage rate: 32%) (*378*). A review concluded that vaccination of HCP in settings in which patients also were vaccinated provided significant reductions in deaths among elderly patients from all causes and deaths from pneumonia (*379*).

Epidemiologic studies of community outbreaks of influenza demonstrate that school-aged children typically have the highest influenza illness attack rates, suggesting routine universal vaccination of children might reduce transmission to their household contacts and possibly others in the community. Results from certain studies have indicated that the benefits of vaccinating children might extend to protection of their adult contacts and to persons at risk for influenza complications in the community. However, these data are limited, and most studies have not used laboratory-confirmed influenza as an outcome measure. A single-blinded, randomized controlled study conducted as part of a 1996–1997 vaccine effectiveness study demonstrated that vaccinating preschool-aged children with TIV reduced influenza-related morbidity among some household contacts (*380*). A randomized, placebo-controlled trial among children with recurrent respiratory tract infections demonstrated that members of families with children who had received a live attenuated virosomal vaccine formulation (not currently available in the United States) were substantially less likely to have respiratory tract infections and reported substantially fewer workdays lost compared with families with children who received placebo (*381*). One cluster randomized trial conducted among rural Hutterite communities in Canada compared laboratory confirmed influenza among unvaccinated persons in communities where children were administered influenza vaccine (coverage: 83%) among children aged 3–15 years with communities where children received hepatitis A vaccine. Influenza vaccine effectiveness for prevention of influenza among unvaccinated persons was 61% (95% CI = 8%–81%) (*382*)

In nonrandomized community-based studies, administration of LAIV has been demonstrated to reduce MAARI (*383,384*) and ILI-related economic and medical consequences (e.g., workdays lost and number of health-care provider visits) among contacts of vaccine recipients (*384*). Households with children attending schools in which school-based LAIV vac-

cination programs had been established reported less ILI and fewer physician visits during peak influenza season compared with households with children in schools in which no LAIV vaccination had been offered. However a decrease in the overall rate of school absenteeism was not reported in communities in which LAIV vaccination was offered (*384*). During an influenza outbreak during the 2005–06 influenza season, countywide school-based influenza vaccination was associated with reduced absenteeism among elementary and high school students in one county that implemented a school-based vaccination program compared with another county without such a program (*385*). These community-based studies have not used laboratory-confirmed influenza as an outcome.

Some studies also have documented reductions in influenza illness among persons living in communities where focused programs for vaccinating children have been conducted. A community-based observational study conducted during the 1968 pandemic using a univalent inactivated vaccine reported that a vaccination program targeting school-aged children (coverage rate: 86%) in one community reduced influenza rates within the community among all age groups compared with another community in which aggressive vaccination was not conducted among school-aged children (*386*). An observational study conducted in Russia demonstrated reductions in ILI among the community-dwelling elderly after implementation of a vaccination program using TIV for children aged 3–6 years (57% coverage achieved) and children and adolescents aged 7–17 years (72% coverage achieved) (*387*). In a nonrandomized community-based study conducted over three influenza seasons, 8%–18% reductions in the incidence of MAARI during the influenza season among adults aged ≥35 years were observed in communities in which LAIV was offered to all children aged ≥18 months (estimated coverage rate: 20%–25%) compared with communities that did not provide routine influenza vaccination programs for all children (*383*). In a subsequent influenza season, the same investigators documented a 9% reduction in MAARI rates during the influenza season among persons aged 35–44 years in intervention communities, where coverage was estimated at 31% among school children. However, MAARI rates among persons aged ≥45 years were lower in the intervention communities regardless of the presence of influenza in the community, suggesting that lower rates could not be attributed to vaccination of school children against influenza (*365*).

The largest study to examine the community effects of increasing overall vaccine coverage was an ecologic study that described the experience in Ontario, Canada, which is the only province to implement a universal influenza vaccination program beginning in 2000. On the basis of models developed from administrative and viral surveillance data, influenza-related mortality, hospitalizations, ED use, and physicians' office visits decreased substantially more in Ontario after program introduction than in other provinces, with the largest reductions observed in younger age groups (*388*). In addition, influenza-associated antibiotic prescriptions were substantially reduced compared with other provinces (*389*).

Efficacy and Effectiveness of Influenza Vaccination When Circulating Influenza Virus Strains Differ from Vaccine Strains

Vaccination can provide reduced but substantial cross-protection against drifted strains in some seasons, including reductions in severe outcomes such as hospitalization. Usually one or more circulating viruses with antigenic changes compared with the vaccine strains are identified in each influenza season. In addition, two distinct lineages of influenza B viruses have co-circulated in recent years, and limited cross-protection is observed against the lineage not represented in the vaccine (*70*). However, assessment of the clinical effectiveness of influenza vaccines cannot be determined solely by laboratory evaluation of the degree of antigenic match between vaccine and circulating strains. In some influenza seasons, circulating influenza viruses with significant antigenic differences predominate, and reductions in vaccine effectiveness sometimes are observed compared with seasons when vaccine and circulating strains are well-matched (*77,170,188,239,289,390*). However, even during years when vaccine strains were not antigenically well-matched to circulating strains (the result of antigenic drift), substantial protection has been observed against severe outcomes, presumably because of vaccine-induced cross-reacting antibodies (*77,188,289,352*). For example, in one study conducted during the 2003–04 influenza season, when the predominant circulating strain was an influenza A (H3N2) virus that was antigenically different from that season's vaccine strain, effectiveness against laboratory-confirmed influenza illness among persons aged 50–64 years was 60% among healthy persons and 48% among persons with medical conditions that increased the risk for influenza complications (*188*). An interim, within-season analysis during the 2007–08 influenza season indicated that vaccine effectiveness was 44% overall, 54% among healthy persons aged 5–49 years, and 58% against influenza A, despite the finding that viruses circulating in the study area were predominately a drifted influenza A (H3N2) and an influenza B strain from a different lineage compared with vaccine strains (*391*). Among children, both TIV and LAIV provide protection against infection even in seasons when vaccines and circulating strains are not well-matched. Vaccine effectiveness against ILI was 49%–69% in two observational

studies, and 49% against medically attended, laboratory-confirmed influenza in a case-control study conducted among young children during the 2003–04 influenza season, when a drifted influenza A (H3N2) strain predominated, based on viral surveillance data (*165,169*). However, the 2009–10 seasonal influenza vaccines provided no protection against medically attended illness caused by the pandemic 2009 influenza A (H1N1) virus, because of substantial changes in key viral antigens compared with recently circulating strains (*392*).

Continued improvements in collecting representative circulating viruses and use of surveillance data to forecast antigenic drift are needed. Manufacturing trivalent influenza virus vaccines is a challenging process that takes 6–8 months to complete. Shortening manufacturing time to increase the time to identify good vaccine candidate strains from among the most recent circulating strains also is important. Data from multiple seasons that are collected in a consistent manner are needed to better understand vaccine effectiveness during seasons when circulating and vaccine virus strains are not well-matched.

Cost-Effectiveness of Influenza Vaccination

Economic studies of influenza vaccination are difficult to compare because they have used different measures of both costs and benefits (e.g., cost-only, cost-effectiveness, cost-benefit, or cost-utility measures). However, most studies indicate that vaccination reduces or minimizes health care, societal, and individual costs and the productivity losses and absenteeism associated with influenza illness. One national study estimated the annual economic burden of seasonal influenza in the United States (using 2003 population and dollars) to be $87.1 billion, including $10.4 billion in direct medical costs (*78*).

Studies of influenza vaccination in the United States among persons aged ≥65 years have estimated substantial reductions in hospitalizations and deaths and overall societal cost savings (*234,235*). A study of a larger population comparing persons aged 50–64 years with those aged ≥65 years estimated the cost-effectiveness of influenza vaccination to be $28,000 per QALY saved (in 2000 dollars) in persons aged 50–64 years compared with $980 per QALY saved among persons aged ≥65 years (*393*).

Economic analyses among adults aged <65 years have reported mixed results regarding influenza vaccination. Two studies in the United States indicated that vaccination can reduce both direct medical costs and indirect costs from work absenteeism and reduced productivity (*79,394*). However, another U.S. study indicated no productivity and absentee savings in a strategy to vaccinate healthy working adults, although vaccination still was estimated to be cost-effective (*395*). In Ontario, Canada, where a universal influenza vaccination program was implemented beginning in 2000, costs were estimated to be approximately twice as much as a targeted vaccination program; however, the number of cases of influenza was reduced 61%, and influenza-related mortality declined 28%, saving an estimated 1,134 QALYs per season overall from a health-care payer perspective. Most cost savings were attributed to the avoidance of hospitalizations. The incremental cost-effectiveness ratio was estimated to be $10,797 Canadian per QALY gained (*396*).

Cost analyses have documented the considerable financial burden of illness among children. In a study of 727 children conducted at a medical center during 2000–2004, the mean total cost of hospitalization for influenza-related illness was $13,159 ($39,792 for patients admitted to an intensive care unit and $7,030 for patients cared for exclusively in the general wards) (*397*). A strategy that focuses on vaccinating children with medical conditions that confer a higher risk for influenza complications are more cost-effective than a strategy of vaccinating all children (*395*). An analysis that compared the costs of vaccinating children of varying ages with TIV and LAIV indicated that costs per QALY saved increased with age for both vaccines. In 2003 dollars per QALY saved, costs for routine vaccination using TIV were $12,000 for healthy children aged 6–23 months and $119,000 for healthy adolescents aged 12–17 years compared with $9,000 and $109,000, respectively, using LAIV (*398*). Economic evaluations of vaccinating children have demonstrated a wide range of cost estimates, but have generally found this strategy to be either cost saving or cost beneficial (*399–402*).

Economic analyses most influenced by the vaccination venue, with vaccination in medical-care settings incurring higher projected costs. In a published model, the mean cost (year 2004 values) of vaccination was lower in mass vaccination ($17.04) and pharmacy ($11.57) settings than in scheduled doctor's office visits ($28.67) (*403*). Vaccination in nonmedical settings was projected to be cost saving for healthy adults aged ≥50 years and for high-risk adults of all ages. For healthy adults aged 18–49 years, preventing an episode of influenza would cost $90 if vaccination were delivered in a pharmacy setting, $210 in a mass vaccination setting, and $870 during a scheduled doctor's office visit (*403*). Medicare and Vaccines for Children program reimbursement rates in recent years have been less than the costs associated with providing vaccination in a medical practice (*404,405*).

Vaccination Coverage Levels

Continued annual monitoring is needed to determine the effects on vaccination coverage of vaccine supply delays and

shortages, changes in influenza vaccination recommendations and target groups for vaccination, reimbursement rates for vaccine and vaccine administration, and other factors. One of the *Healthy People 2010* objectives (objective no. 14-29a) includes achieving an influenza vaccination coverage level of 90% for persons aged ≥65 years and among nursing home residents (*406,407*); new strategies to improve coverage are needed to achieve this objective (*408,409*).

On the basis of 2009 final data and 2010 early release data from the National Health Interview Survey (NHIS), estimated national influenza vaccine coverage during the 2007–08 and 2008–09 influenza seasons did not increase substantially among persons aged ≥65 years and those aged 50–64 years (Table 3) and are only slightly higher than coverage levels observed before the 2004–05 vaccine shortage year (*410–412*). In the 2007–08 and 2008–09 influenza seasons, estimated vaccination coverage levels (based on NHIS data) among adults with high-risk conditions aged 18–49 years were 30.4% and 33%, respectively, substantially lower than the *Healthy People 2000* and *Healthy People 2010* objectives of 60% (Table 3) (*406,407*). Among adults with asthma aged 18–49 years and 50–64 years, estimated coverage during the 2006–07 influenza season was 24% and 55% respectively; the national objective for coverage among adults with asthma is 60% (*413*). Epidemiologic studies conducted during the 2009 pandemic indicated that more hospitalizations and deaths were occurring among adults aged <65 years with high-risk conditions than among any other group, and these adults were among the initial target groups to receive the 2009 H1N1 vaccination while vaccine supply was limited (*414*). However, coverage among adults aged <65 years with medical conditions that confer a higher risk for influenza complications was <40% for the 2009 H1N1 monovalent vaccine (*415*).

During the 2009 influenza A (H1N1) pandemic, state-level estimates of seasonal vaccine coverage data for both seasonal influenza and the monovalent 2009 H1N1 vaccines were obtained via telephone surveys conducted by the Behavioral Risk Factor Surveillance System (BRFSS) and the National 2009 H1N1 Flu Survey. By January 31, 2010 estimated state seasonal influenza vaccination coverage among persons aged ≥6 months ranged from 30.3% to 54.5% (median: 40.6%). Median coverage was 41.2% for children aged 6 months–17 years, 38.3% for adults aged 18–49 years with high-risk conditions, 28.8% for adults aged 18–49 years without high-risk conditions, 45.5% for adults aged 50–64 years, and 69.3% for adults aged ≥65 years. These results, compared with the previous season, suggest large increases in coverage for children and a moderate increase for adults aged 18–49 years without high-risk compared with seasonal influenza vaccine coverage estimates in previous seasons (*415,416*). However, vaccine coverage estimates using BRFSS data typically have been higher than estimates derived from NHIS data (*416*).

Studies conducted among children and adults indicate that opportunities to vaccinate persons at risk for influenza complications (e.g., during hospitalizations for other causes) often are missed. In one study, 23% of children hospitalized with influenza and a comorbidity had a previous hospitalization during the preceding influenza vaccination season (*417*). In a study of hospitalized Medicare patients, only 31.6% were vaccinated before admission, 1.9% during admission, and 10.6% after admission (*418*). A study in New York City conducted during 2001–2005 among 7,063 children aged 6–23 months indicated that 2-dose vaccine coverage increased from 1.6% to 23.7% over time; however, although the average number of medical visits during which an opportunity to be vaccinated decreased during the course of the study from 2.9 to 2.0 per child, 55% of all visits during the final year of the study still represented a missed vaccination opportunity (*419*). Using standing orders in hospitals increases vaccination rates among hospitalized persons (*420*), and vaccination of hospitalized patients is safe and stimulates an appropriate immune response (*220*). In one survey, the strongest predictor of receiving vaccination was the survey respondent's belief that he or she was in a high-risk group, based on data from one survey; however, many persons in high-risk groups did not know that they were in a group recommended for vaccination (*421,422*). In one study, over half of adults who did not receive influenza vaccination reported that they would have received vaccine if this had been recommended by their health-care provider (*422*).

Reducing racial/ethnic health disparities, including disparities in influenza vaccination coverage, is an overarching national goal that is not being met (*407*). Estimated vaccination coverage levels in 2008 among persons aged ≥65 years were 70% for non-Hispanic whites, 52% for non-Hispanic blacks, and 52% for Hispanics (*423*). Among Medicare beneficiaries, other key factors that contribute to disparities in coverage include variations in the propensity of patients to actively seek vaccination and variations in the likelihood that providers recommend vaccination (*424,425*). One study estimated that eliminating these disparities in vaccination coverage would have an impact on mortality similar to the impact of eliminating deaths attributable to kidney disease among blacks or liver disease among Hispanics (*426*). Differences in coverage by race or ethnicity might be partly attributable to differences in beliefs about vaccine effectiveness and safety (*422*). Among nursing home patients, fewer blacks and Hispanics are offered vaccine or receive it compared with whites, and blacks refuse vaccination more frequently (*427*). Disparities in seasonal influenza vaccine coverage among adult whites (43%), blacks (31%), and Hispanics (31%) also were observed during 2009–2010 (*416*).

TABLE 3. Influenza vaccination* coverage levels for the 2006–07, 2007–08, and 2008–09 influenza seasons, among population groups — National Health Interview Survey (NHIS), United States, 2007–2009, and National Immunization Survey (NIS), 2006–2008.

Population Group	2006–07 season			2007–08 season			2008–09 season		
	Crude sample size†	Influenza vaccination level		Crude sample size	Influenza vaccination level		Crude sample size	Influenza vaccination level	
		%	(95% CI§)		%	(95% CI)		%	(95% CI)
Persons with an age indication									
Aged 6–23 mos (NIS¶)	9,710	31.8	(30.2–33.4)	11964	40.7	(39.1–42.2)	NA**	NA	NA
Aged 2–4 yrs	853	37.9	(34.2–41.7)	674	40.3	(35.8–45.0)	652	41.8)	(36.5–47.4)
Aged 50–64 yrs	3,746	36.0	(34.0–38.0)	3,258	38.4	(36.4–40.4)	3,136	40.1	(37.9–42.3)
Aged ≥65 yrs	3,086	65.6	(63.3–67.9)	2,658	66.3	(64.2–68.3)	2,455	65.5	(63.2–67.8)
Persons with high-risk conditions††									
Aged 5–17 yrs	387	33.0	(26.2–40.7)	262	36.2	(29.3–43.6)	273	34.7	(27.8–42.3)
Aged 18–49 yrs	1,186	25.5	(22.4–28.9)	1,049	30.4	(27.1–34.0)	1,087	33.0	(29.7–36.4)
Aged 50–64 yrs	1,117	46.1	(42.8–49.4)	1,001	48.4	(44.7–52.2)	1,048	51.3	(47.2–55.3)
Aged 18–64 yrs	2,303	35.3	(33.0–37.7)	2,050	38.8	(36.2–41.4)	2,135	42.0	(39.3–44.6)
Persons without high–risk conditions									
Aged 5–17 yrs	3,307	17.5	(15.9–19.2)	2,925	21.1	(19.3–23.1)	2,906	24.6	(22.4–26.9)
Aged 18–49 yrs	7,905	15.3	(14.2–16.4)	6,467	17.0	(15.7–18.3)	6,083	19.3	(18.1–20.7)
Aged 50–64 yrs	2,619	31.8	(29.5–34.1)	2,248	34.1	(31.7-36.6)	2,083	34.3	(31.8–36.9)
Pregnant women§§	177	13.4	(8.5–20.5)	113	24.2	(15.1–36.6)	177	11.3	(6.4–19.0)
Health-care workers¶¶	850	44.4	(40.2–48.7)	1,037	49.0	(45.1–52.8)	NA	NA	NA
Household contacts of persons at high risk, including children aged <5 years* **									
Aged 5–17 yrs	741	26.0	(21.5–31.1)	968	24.8	(21.4–28.6)	997	26.0	(23.6–30.3)
Aged 18–49 yrs	1,349	17.0	(15.0–19.4)	1,753	19.5	(17.1–22.1)	1,775	23.7	(21.4–26.2)

* Answered yes to this question, "During the past 12 months, have you had a flu shot (flu spray)," and answered the follow-up question "What was the month and year of your most recent shot (spray), which were asked during a face-to-face interview conducted any day during March through August.

† Population sizes by subgroups are available at http://www.cdc.gov/flu/professionals/vaccination/pdf/influenza_vaccine_target_populations.pdf.

§ 95% confidence interval.

¶ NIS uses provider-verified vaccination status to improve the accuracy of the estimate. The NIS estimate for the 2008–09 season will be available summer or fall 2010.

** Data not yet available.

†† Adults categorized as being at high risk for influenza-related complications self-reported one or more of the following: 1) ever being told by a physician they had diabetes, emphysema, coronary heart disease, angina, heart attack, or other heart condition; 2) having a diagnosis of cancer during the preaceding 12 months (excluding nonmelanoma skin cancer) or ever being told by a physician they have lymphoma, leukemia, or blood cancer during the previous 12 months (postcoding for a cancer diagnosis was not yet completed at the time of this publication so this diagnosis was not included in the 2006–07 season data.); 3) being told by a physician they have chronic bronchitis or weak or failing kidneys; or 4) reporting an asthma episode or attack during the preceding 12 months. For children aged <18 years, high-risk conditions included ever having been told by a physician of having diabetes, cystic fibrosis, sickle cell anemia, congenital heart disease, other heart disease, or neuromuscular conditions (seizures, cerebral palsy, and muscular dystrophy), or having an asthma episode or attack during the preceding 12 months.

§§ Aged 18–44 years, pregnant at the time of the survey, and without high-risk conditions.

¶¶ Adults were classified as health-care workers if they were currently employed in a health-care occupation or in a health-care–industry setting, on the basis of standard occupation and industry categories recoded in groups by CDC's National Center for Health Statistics.

*** Interviewed sample child or adult in each household containing at least one of the following: a child aged <5 years, an adult aged ≥65 years, or any person aged 5–17 years at high risk (as defined in previous footnote for adults at high risk). To obtain information on household composition and high-risk status of household members, the sampled adult, child, and person files from NHIS were merged. Interviewed adults who were health-care workers or who had high-risk conditions were excluded. Information could not be assessed regarding high-risk status of other adults aged 18–64 years in the household; therefore, certain adults aged 18–64 years who live with an adult aged 18–64 years at high risk were not included in the analysis. Also note that although the recommendation for children aged 2–4 years was not in place during the 2005–06 season, children aged 2–4 years were included in these calculations as if the recommendation already was in place to facilitate comparison of coverage data for subsequent years.

Reported vaccination levels are low among children at increased risk for influenza complications. Coverage among children aged 2–17 years with asthma was estimated to be 29% for the 2004–05 influenza season (*428*). During the 2007–08 influenza season, the fourth season for which ACIP recommended that all children aged 6–23 months receive vaccination, National Immunization Survey data demonstrated that 41% of children aged 6–23 months received at least 1 dose of influenza vaccine, and 23% were fully vaccinated (i.e., received 1 or 2 doses depending on previous vaccination history); however, results varied substantially among states (*429*). Data from the eight Immunization Information System sentinel sites during 2008–09 indicated that 48% of children aged 6–23 months had received at least 1 dose, and 29% were fully vaccinated (*430*). Coverage levels in these sites for older children were lower and declined with increasing age, ranging from 22% fully vaccinated among children aged 2–4 years to 9% among children aged 13–18 years (*430*). As has been reported for older adults, a physician recommendation for vaccination and the perception that having a child be vaccinated

"is a smart idea" were associated positively with likelihood of vaccination of children aged 6–23 months (*431*). Similarly, children with asthma were more likely to be vaccinated if their parents recalled a physician recommendation to be vaccinated or believed that the vaccine worked well (*432*). Implementation of a reminder/recall system in a pediatric clinic increased the percentage of children with asthma receiving vaccination from 5% to 32% (*433*). Reminder/recall systems might be particularly useful when limited vaccine availability requires targeted vaccination of children with high-risk conditions (*434*).

Although annual vaccination is recommended for HCP and is a high priority for reducing morbidity associated with influenza in health-care settings and for expanding influenza vaccine use (*435–437*), NHIS data demonstrated a vaccination coverage level of only 44.4% among HCP during the 2006–07 season, and 49% during the 2007–08 season (Table 3). Coverage levels during the 2009 pandemic were higher for seasonal vaccine, but remained low for the 2009 pandemic vaccine. By mid-January 2010, estimated vaccination coverage among HCP was 37% for 2009 pandemic influenza A (H1N1) and 62% for seasonal influenza, based on a RAND Corporation–conducted telephone survey that used a somewhat different methodology than NHIS (*438*). Overall, 64% received either of these influenza vaccines, higher coverage than any previous season, but only 35% of HCP reported receiving both vaccines (*438*). Vaccination of HCP has been associated with reduced work absenteeism (*370*) and with fewer deaths among nursing home patients (*375,377*) and elderly hospitalized patients (*379*). Factors associated with a higher rate of influenza vaccination among HCP include older age, being a hospital employee, having employer-provided health-care insurance, having had pneumococcal or hepatitis B vaccination in the past, or having visited a health-care professional during the preceding year. HCP who decline vaccination frequently express doubts about the risk for influenza and the need for vaccination, are concerned about vaccine effectiveness and side effects, and dislike injections (*439*).

Vaccine coverage among pregnant women increased during the 2007–08 influenza season, with 24% of pregnant women reporting vaccination, excluding pregnant women who reported diabetes, heart disease, lung disease, and other selected high-risk conditions; seasonal vaccine coverage estimates for 2008–09 were only 11%, however, which is closer to pre-2007 estimates and likely reflects variation in estimates caused by the small sample size rather than significant fluctuations in coverage (Table 3). The causes of persistent low coverage among pregnant women are not fully determined. However, in a study of influenza vaccination acceptance by pregnant women, 71% of those who were offered the vaccine chose to be vaccinated (*440*). However, a 1999 survey of obstetricians and gynecologists determined that only 39% administered influenza vaccine to obstetric patients in their practices, although 86% agreed that pregnant women's risk for influenza-related morbidity and mortality increases during the last two trimesters (*441*). Pregnancy was an important risk factor during the 2009 H1N1 pandemic (*106,120*), and because the 2009 H1N1 influenza virus is expected to continue circulation during 2010–11, improved vaccination coverage among pregnant women is needed.

Influenza vaccination coverage in all groups recommended for vaccination remains suboptimal. Despite the timing of the peak of influenza disease, administration of vaccine decreases substantially after November. According to results from NHIS, for the three most recent influenza seasons for which these data are available, approximately 84% of all influenza vaccinations were administered during September–November. Among persons aged ≥65 years, the percentage of September–November vaccinations was 92% (*442*). Because many persons recommended for vaccination remain unvaccinated at the end of November, CDC encourages public health partners and health-care providers to conduct vaccination clinics and other activities that promote seasonal influenza vaccination annually during National Influenza Vaccination Week (December 6–12, 2010) and throughout the remainder of the influenza season.

Self-report of influenza vaccination among adults compared with determining vaccination status from the medical record, is a sensitive and specific source of information (*443*). Patient self-reports should be accepted as evidence of influenza vaccination in clinical practice (*443*). However, information on the validity of parents' reports of pediatric influenza vaccination is not yet available.

Vaccination coverage estimates for the influenza A (H1N1) 2009 monovalent vaccines indicate that most doses were administered to the initial target groups, and that, by January 2, 2010 (approximately 90 days after vaccine first became available), an estimated 20% of the U.S. population (61 million persons) had been vaccinated, including 28% of persons in the initial target groups. An estimated 30% of U.S. children aged 6 months–18 years had been vaccinated, including 33% of children aged 6 months–4 years. Estimated coverage for specific initial target groups was 38% for pregnant women, 22% for HCP, and 12% for adults aged 25–64 years with medical conditions that confer a higher risk for influenza complications. Estimates of 2009 H1N1 vaccination coverage levels generally were higher among non-Hispanic whites than among non-Hispanic blacks (*438*). These coverage estimates were in the same approximate range as estimates for seasonal vaccination coverage, suggesting that concerns about the pandemic were not sufficient to overcome some barriers to influenza vaccination among persons at higher risk for influenza complications.

Recommendations for Using TIV and LAIV During the 2010–11 Influenza Season

Routine vaccination of all persons aged ≥6 months is recommended. During the 2009–10 influenza season, an estimated 85% of the U.S. population already had an indication for vaccination (*444*). A universal vaccination recommendation for all persons aged ≥6 months eliminates the need to determine whether each person has an indication for vaccination and emphasizes the importance of preventing influenza among person of all ages. The expansion of recommendations for annual vaccination to include all adults is supported by evidence that influenza vaccines are safe and effective. In addition, morbidity and mortality among adults aged <50 years, including adults who were previously healthy, occurs in every influenza season. Although most adults in this age group who develop influenza-related complications have medical risk factors, some have no previously identified risk factors for influenza complications, or have risk factors but are unaware that they should be vaccinated. Expansion of vaccination recommendations to all adults reflects the need to remove potential barriers to receipt of influenza vaccine, including lack of awareness about vaccine indications among persons at higher risk for influenza complications and their close contacts. Although the capacity now exists to produce sufficient influenza vaccines to meet the predicted increase in demand, the annual supply of influenza vaccine and timing of its distribution cannot be guaranteed in any year.

Further support for expansion of recommendations to include all adults is based on data from the 2009 pandemic experience. Data from epidemiologic studies conducted during the 2009 influenza A (H1N1) pandemic indicates that the risk for influenza complications among adults aged <50 years who had 2009 pandemic influenza A (H1N1) is greater than is typically seen for seasonal influenza (*12*). Explosive outbreaks of 2009 H1N1 influenza among young adults in settings such as college campuses (*445*) were part of the basis for prioritizing vaccination of all persons aged 6 months–24 years during the 2009 pandemic influenza response. Pandemic 2009 influenza A (H1N1)-like viruses are expected to continue to circulate during the 2010–11 influenza season, and a substantial proportion of young adults do not yet have immunity as a result of natural infection with this virus (*446*). In addition, severe infections were observed more frequently in some younger adults who did not have previously recognized risk factors for influenza-related complications, including obese persons, persons in certain racial and ethnic minority groups, and postpartum women (*24,48,85,86,90,447*).

Both TIV and LAIV prepared for the 2010–11 season will include A/California/7/2009 (H1N1)-like, A/Perth/16/2009 (H3N2)-like, and B/Brisbane/60/2008-like antigens. The influenza B virus component of the 2010–11 vaccine is from the Victoria lineage (*448*). These viruses will be used because they are representative of influenza viruses that are predicted to be circulating in the United States during the 2010–11 influenza season and have favorable growth properties in eggs. The H1N1 strain recommended for the 2010–11 trivalent influenza vaccine is the same as the vaccine strain in the 2009 H1N1 monovalent vaccines given during the pandemic. The 2009 pandemic influenza virus-derived vaccine strain has replaced the seasonal influenza H1N1 vaccine strains that were present in the vaccine since 1977.

Healthy nonpregnant persons aged 2–49 years can choose to receive either TIV or LAIV. Some TIV formulations are FDA-licensed for use in persons as young as age 6 months (see Recommended Vaccines for Different Age Groups). Persons aged ≥65 years can be administered either standard-dose TIV 15 mcg per vaccine strain) or the newly licensed TIV containing 60 mcg HA antigen per vaccine strain (Sanofi pasteur). TIV is licensed for use in persons with high-risk conditions (Table 2). LAIV is FDA-licensed for use only for persons aged 2–49 years. In addition, FDA has indicated that the safety of LAIV has not been established in persons with underlying medical conditions that confer a higher risk for influenza complications.

All children aged 6 months–8 years who have not been vaccinated previously at any time with at least 1 dose of either LAIV (if appropriate) or TIV should receive 2 doses of age-appropriate vaccine in the same season, with a single dose during subsequent seasons. Persons who received a 2009 H1N1 monovalent vaccine should still be vaccinated with the 2010–11 formulation of TIV or LAIV to provide protection against influenza A (H3N2) and influenza B strains that are expected to circulate during the 2010–11 influenza season. In addition, the duration of protection after receipt of the 2009 H1N1 monovalent influenza vaccines is unknown and likely declines over time.

In addition, emphasis on providing routine vaccination annually to certain groups at higher risk for influenza infection or complications is advised, including all children aged 6 months–18 years, all persons aged ≥50 years, and other persons at risk for medical complications from influenza. These persons, their household and close contacts, and all HCP should continue to be a focus of vaccination efforts as providers and programs transition to routinely vaccinating all persons aged ≥6 months (Box). Despite a recommendation for vaccination for approximately 85% of the U.S. population over the past

two seasons, <50% of the U.S. population received a seasonal influenza vaccination in 2008–09 or 2009–10. Estimated vaccine coverage for the 2009 H1N1 monovalent vaccine coverage was <40% (*438*).

Rationale for Vaccination of Specific Populations

Children Aged 6 Months–18 Years

Annual vaccination for all children aged 6 months–18 years is recommended. Healthy children aged 2–18 years can receive either LAIV or TIV. Children aged 6–23 months, and those aged 2–4 years who have evidence of asthma, wheezing, or who have medical conditions that put them at higher risk for influenza complications should receive TIV (see Considerations When Using LAIV).

Recommendations to provide routine influenza vaccination to all children and adolescents aged 6 months–18 years are made on the basis of 1) accumulated evidence that influenza vaccine is effective and safe for children (see Influenza Vaccine Efficacy, Effectiveness, and Safety); 2) increased evidence that influenza has substantial adverse impacts among children and their contacts (e.g., school absenteeism, increased antibiotic use, medical care visits, and parental work loss) (see Health-Care Use, Hospitalizations, and Deaths Attributed to Influenza); and 3) an expectation that a simplified age-based influenza vaccine recommendation for all children and adolescents will improve vaccine coverage levels among children who already have a risk- or contact-based indication for annual influenza vaccination.

Children typically have the highest attack rates during community outbreaks of influenza and serve as a major source of transmission within communities (*1,2*). If sufficient vaccination coverage among children can be achieved, potential benefits include the indirect effect of reducing influenza among persons who have close contact with children and reducing overall transmission within communities (*449*). Achieving and sustaining community-level reductions in influenza will require mobilization of community resources and development of sustainable annual vaccination campaigns to assist health-care providers and vaccination programs in providing influenza vaccination services to children of all ages. In many areas, innovative community-based efforts, which might include mass vaccination programs in school or other community settings, will be needed to supplement vaccination services provided in health-care providers' offices or public health clinics. In nonrandomized community-based controlled trials, reductions in ILI-related symptoms and medical visits among household contacts have been demonstrated in communities where vaccination programs among school-aged children were established compared with communities without such vaccination programs (*365,386,387*).

All children aged 6 months–8 years who receive a seasonal influenza vaccine for the first time should be administered 2 doses. Children aged 6 months–8 years who received a seasonal vaccine for the first time during 2009–2010 but who received only 1 dose should receive 2 doses, rather than 1, during 2010–2011. In addition, for the 2010–11 influenza season, children aged 6 months–8 years who did not receive at least 1 dose of an influenza A (H1N1) 2009 monovalent vaccine should receive 2 doses of a 2010–11 seasonal influenza vaccine, regardless of previous influenza vaccination history (Figure 3). Children aged 6 months–8 years for whom the previous 2009–10 seasonal or influenza A (H1N1) 2009 monovalent vaccine history cannot be determined should receive 2 doses of a 2010–11 seasonal influenza vaccine. For all children, the second dose of a recommended 2-dose series should be administered ≥4 weeks after the initial dose.

The recommendation to administer 2 doses to children who did not receive an influenza A (H1N1) 2009 monovalent vaccine, regardless of previous seasonal influenza vaccine history, is new. This change in recommendations is made on the basis of data from several immunogenicity studies indicating that children aged <9 years have lower antibody levels and lower rates of protective response after receiving a single dose of vaccines containing the 2009 pandemic H1N1 antigen compared with older children and adults. However, >80% of infants and children aged <3 years and >90% of older children who receive 2 doses of a vaccine that contains the 2009 H1N1 antigen develop protective antibody levels (*158,160*; National Institutes of Health, unpublished data, 2010). Therefore, current immunogonicity data indicate that at least 2 doses of the 2009 H1N1 vaccine antigen are needed to produce protective antibody levels for the majority of young children. This recommendation includes children who have received at least 2 doses of a seasonal influenza vaccine in a previous season and who would normally be scheduled to only receive 1 seasonal vaccine dose in the 2010–11 season.

A second dose is not necessary for children being vaccinated for the first time who were aged 8 years at the time of the first dose but who are seen again after they have reached age 9 years. Children aged 6 months–8 years who had never received a seasonal influenza vaccine previously and who received only the 2009 H1N1 monovalent vaccine should receive 2 doses of the 2010–11 seasonal influenza vaccine, to provide adequate protection against influenza A (H3N2) and influenza B. If possible, children recommended for 2 doses of seasonal influenza

Please note: An erratum has been published for this issue. To view the erratum, please click here.

FIGURE 3. Number of 2010–2011 seasonal influenza vaccine doses recommended for children

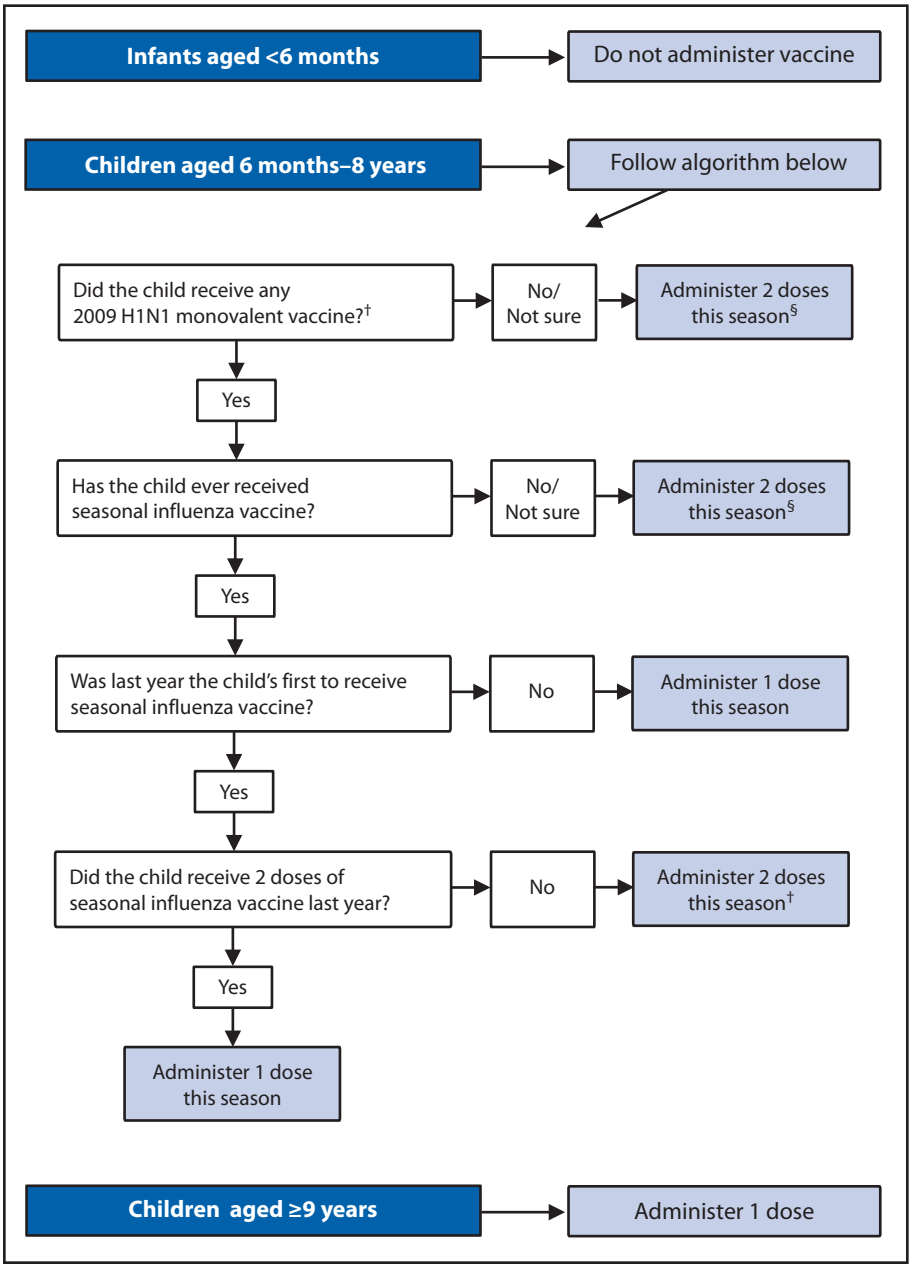


*Figure developed by CDC with the American Academy of Pediatrics, Committee on Infectious Diseases.

† Children who had a laboratory-confirmed 2009 pandemic H1N1 virus infection (e.g., reverse transcription–polymerase chain reaction or virus culture specific for 2009 pandemic influenza A(H1N1) virus) are likely to be immune to this virus. At provider discretion, these children can have a "Yes" entered at this box, and proceed down the path to the next box to determine whether two doses are indicated based on seasonal vaccine history. However, if no test result is available and no influenza A(H1N1) 2009 monovalent vaccine was administered, enter "no" here.

§ Interval between 2 doses is ≥4 weeks.

vaccine should receive them both before onset of influenza season. However, vaccination, including the second dose, is recommended even after influenza virus begins to circulate in a community.

Children who had a laboratory-confirmed 2009 pandemic influenza A (H1N1) virus infection (e.g., reverse transcription–PCR or virus culture specific for 2009 pandemic influenza A (H1N1) virus) are likely to be immune to this virus. There is no known harm in providing 2 doses of 2010–11 seasonal influenza vaccine to a child who has been infected previously with the 2009 pandemic influenza A (H1N1) virus. However, at immunization provider discretion, these children can receive the appropriate number of seasonal vaccine doses (1 or 2) without regard to previous receipt of the influenza A (H1N1) 2009 monovalent vaccine. However, most children did not receive specific diagnostic testing (i.e., were untested or received a rapid antigen test), and for others, evidence of laboratory confirmation using a diagnostic test specific for the 2009 H1N1 antigen is unavailable to immunization providers. If no test results are available and no influenza A (H1N1) 2009 monovalent vaccine had been administered, children who had a febrile respiratory illness during 2009–2010 cannot be assumed to have had influenza A (H1N1) virus infection, and these children should receive 2 doses of the 2010–11 seasonal vaccine. Providers who are determining the number of vaccine doses recommended for children with laboratory-confirmed 2009 pandemic influenza A (H1N1) virus infection (Figure 3) should also determine whether 2 doses are indicated on the basis of seasonal vaccine history.

Persons at Risk for Medical Complications

Vaccination to prevent influenza is particularly important for persons who are at increased risk for severe complications from influenza or at higher risk for influenza-related outpatient, ED, or hospital visits. When vaccine supply is limited, vaccination

efforts should focus on delivering vaccination to the following persons:

- all children aged 6 months–4 years (59 months);
- all persons aged ≥50 years;
- adults and children who have chronic pulmonary (including asthma) or cardiovascular (except isolated hypertension), renal, hepatic, neurological, hematologic, or metabolic disorders (including diabetes mellitus);
- persons who have immunosuppression (including immunosuppression caused by medications or by HIV);
- women who are or will be pregnant during the influenza season;
- children and adolescents (aged 6 months–18 years) who are receiving long-term aspirin therapy and who might be at risk for experiencing Reye syndrome after influenza virus infection;
- residents of nursing homes and other long-term–care facilities;
- American Indians/Alaska Natives;
- persons who are morbidly obese (BMI ≥40);
- HCP;
- household contacts and caregivers of children aged <5 years and adults aged ≥50 years, with particular emphasis on vaccinating contacts of children aged <6 months; and
- household contacts and caregivers of persons with medical conditions that put them at higher risk for severe complications from influenza.

For children, the risk for severe complications from influenza is highest among those aged <2 years, who have much higher rates of hospitalization for influenza-related complications compared with older children (*7,54,61*). Medical care and ED visits attributable to influenza are increased among children aged <5 years compared with older children (*54*). Chronic neurologic conditions are thought to place persons at higher risk for influenza complications on the basis of the potential for compromised respiratory function or the handling of respiratory secretions, both of which can increase the risk for aspiration; such conditions include cognitive dysfunction, spinal cord injuries, seizure disorders, or neuromuscular disorders (*46*).

An observational study conducted during the 2009 H1N1 pandemic indicated that morbid obesity, and possibly obesity, might be a new or previously unrecognized risk factor for influenza-related complications (*85*). In another study, American Indians/Alaska Natives were demonstrated to have a higher risk for death from 2009 H1N1 influenza (*90*). These medical and race/ethnicity risk factors might reflect a higher prevalence of underlying chronic medical conditions, including conditions that are not known by the patient or provider. Other minority groups, including blacks, have been demonstrated to have higher incidence of hospitalizations as a result of laboratory-confirmed influenza compared with whites (CDC, unpublished data, 2010); additional study is needed to determine the reasons. Persons who have chronic medical conditions, who are pregnant, or who are at higher risk for 2009 H1N1 influenza-related complications should be encouraged to begin receiving a routine annual influenza vaccination as programs and practitioners transition to providing vaccination for all persons aged ≥6 months (Box).

Persons Who Live With or Care for Persons at Higher Risk for Influenza-Related Complications

All persons aged ≥6 months should be vaccinated annually. As providers and programs transition to providing annual vaccination to all persons, continued emphasis should be placed on vaccination of persons who live with or care for persons at higher risk for influenza-relate complications. When vaccine supply is limited, vaccination efforts should focus on delivering vaccination to persons at higher risk for influenza-related complications as well as these persons:

- HCP;
- household contacts (including children) and caregivers of children aged ≤59 months (i.e., aged <5 years) and adults aged ≥50 years; and
- household contacts (including children) and caregivers of persons with medical conditions that put them at higher risk for severe complications from influenza.

Healthy persons who are infected with influenza virus, including those with subclinical infection, can transmit influenza virus to persons at higher risk for complications from influenza. In addition to HCP, groups that can transmit influenza to high-risk persons include:

- employees of assisted living and other residences for persons in groups at high risk;
- persons who provide home care to persons in groups at high risk; and
- household contacts of persons in groups at high risk, including contacts such as children or mothers of newborns.

In addition, because children aged <5 years are at increased risk for influenza-related hospitalization (*7,47,61,450,451*) compared with older children, vaccination is recommended for their household contacts and out-of-home caregivers. Because influenza vaccines have not been licensed by FDA for use among children aged <6 months, emphasis should be placed on vaccinating contacts of these children.

Healthy HCP and persons aged 2–49 years who are contacts of persons in these groups and who are not contacts of severely immunocompromised persons living in a protected

environment (see Close Contacts of Immunocompromised Persons) should receive either LAIV or TIV when indicated or requested. All other persons, including pregnant women, should receive TIV.

All HCP and persons in training for health-care professions should be vaccinated annually against influenza. Persons working in health-care settings who should be vaccinated include physicians, nurses, and other workers in both hospital and outpatient-care settings, medical emergency–response workers (e.g., paramedics and emergency medical technicians), employees of nursing home and long-term–care facilities who have contact with patients or residents, and students in these professions who will have contact with patients (*436,437,452*).

Facilities that employ HCP should provide vaccine to workers by using approaches that have been demonstrated to be effective in increasing vaccination coverage. The HCP influenza coverage goal should be vaccination of 100% of employees who do not have medical contraindications. Health-care administrators should consider the level of vaccination coverage among HCP to be one measure of a patient safety quality program and consider obtaining signed declinations from personnel who decline influenza vaccination for reasons other than medical contraindications (*437,453,454*). Influenza vaccination rates among HCP within facilities should be measured regularly and reported, and ward-, unit-, and specialty-specific coverage rates should be provided to staff and administration (*437*).

Policies that work best to achieve this coverage goal might vary among facilities. Studies have demonstrated that organized campaigns can attain higher rates of vaccination among HCP with moderate effort and by using strategies that increase vaccine acceptance (*435,437,455,456*). A mandatory influenza vaccination policy for HCP, exempting only those with a medical contraindication, has been demonstrated to be a highly effective approach to achieving high vaccine coverage among HCP (*456–458*). Hospitals and health-care systems that have mandated vaccination of HCP often have achieved coverage rates of >90%, and persons refusing vaccination who do not have a medical contraindication have been required to wear a surgical mask during influenza season in some programs (*458*). Efforts to increase vaccination coverage among HCP using mandatory vaccination policies are supported by various national accrediting and professional organizations, including the Infectious Diseases Society of America, and in certain states by statute (*457,459,460*). Worker objections, including legal challenges, are an important consideration for facilities considering mandates (*459,461*). Studies to assess the impact of mandatory HCP vaccination on patient outcomes are needed.

The Joint Commission on Accreditation of Health-Care Organizations has approved an infection-control standard that requires accredited organizations to offer influenza vaccinations to staff, including volunteers and licensed independent practitioners with close patient contact. The standard became an accreditation requirement beginning January 1, 2007 (*462*). Some states have regulations regarding vaccination of HCP in long-term–care facilities (*463*), require that health-care facilities offer influenza vaccination to HCP, or require that HCP either receive influenza vaccination or indicate a religious, medical, or philosophic reason for not being vaccinated (*464,465*).

Children aged <6 months are not recommended for vaccination, and antivirals are not licensed for use among infants. Protection of young infants, who have hospitalization rates similar to those observed among the elderly, depends on vaccination of the infants' close contacts. A recent study conducted in Bangladesh demonstrated that infants born to vaccinated women have significant protection from laboratory-confirmed influenza, either through transfer of influenza-specific maternal antibodies or by reducing the risk for exposure to influenza that might occur through vaccination of the mother (*217*). All household contacts, health-care and day care providers, and other close contacts of young infants should be vaccinated.

Immunocompromised persons are at risk for influenza complications but might have inadequate protection after vaccination. Vaccination of close contacts of immunocompromised persons, including HCP, might reduce the risk for influenza transmission. In 2006, a joint recommendation from ACIP and the Hospital Infection Control Practices Advisory Committee (HICPAC) recommended that TIV be used for vaccinating household members, HCP, and others who have close contact with severely immunosuppressed persons (e.g., patients with hematopoietic stem cell transplants) during those periods in which the immunosuppressed person requires care in a protective environment (typically defined as a specialized patient-care area with a positive airflow relative to the corridor, high-efficiency particulate air filtration, and frequent air changes) (*437,466*). To reduce the theoretic risk for vaccine virus transmission, ACIP/HICPAC recommended that HCP who receive LAIV should avoid providing care for severely immunosuppressed patients requiring a protected environment for 7 days after vaccination, and hospital visitors who have received LAIV should avoid contact with severely immunosuppressed persons in protected environments for 7 days after vaccination but should not be restricted from visiting less severely immunosuppressed patients. Healthy nonpregnant persons aged 2–49 years, including HCP, who have close contact with persons with lesser degrees of immunosuppression (e.g., persons with chronic immunocompromising conditions such as HIV infection, corticosteroid or chemotherapeutic medication use, or who are cared for in other hospital areas such as neonatal intensive care units) can receive TIV or LAIV.

The rationale for avoiding use of LAIV among HCP or other close contacts of severely immunocompromised patients is the theoretic risk that a live attenuated vaccine virus could be transmitted to the severely immunosuppressed person. However, instances of LAIV transmission from a recently vaccinated person to an immunocompromised contact in health-care settings have not been reported. In addition, the temperature-sensitive and attenuated viruses present in LAIV do not cause illness when administered to immunocompromised persons with HIV infection (*336*), children undergoing cancer treatment (*467*), or immunocompromised ferrets given dexamethasone and cytarabine (*468*). Concerns about the theoretic risk posed by transmission of live attenuated vaccine viruses contained in LAIV to patients should not be used to justify preferential use of TIV in health-care settings other than inpatient units that house severely immunocompromised patients requiring protected environments. Some health-care facilities might choose to not restrict use of LAIV in close contacts of severely immunocompromised persons, based on the lack of evidence for transmission in health-care settings since licensure in 2004.

Pregnant and Postpartum Women

Vaccination of pregnant women protects women and newborns. The American College of Obstetricians and Gynecologists and the American Academy of Family Physicians also have previously recommended routine vaccination of all pregnant women (*469*). Women who are postpartum are also at risk for influenza complications and should be vaccinated (*108*). No preference is indicated for use of TIV that does not contain thimerosal as a preservative (see Vaccine Preservative [Thimerosal] in Multidose Vials of TIV) for any group recommended for vaccination, including pregnant and postpartum women. LAIV is not licensed for use in pregnant women, but postpartum women can receive LAIV or TIV. Pregnant and postpartum women do not need to avoid contact with persons recently vaccinated with LAIV.

Breastfeeding Mothers

Breastfeeding does not affect the immune response adversely and is not a contraindication for vaccination (*246*). Unless contraindicated because of other medical conditions, women who are breastfeeding can receive either TIV or LAIV. In one randomized controlled trial conducted in Bangladesh, infants born to women vaccinated during pregnancy had a lower risk for laboratory-confirmed influenza. However, the contribution to protection from influenza of breastfeeding compared with passive transfer of maternal antibodies during pregnancy was not determined (*217*).

Travelers

The risk for exposure to influenza during travel depends on the time of year and destination. In the temperate regions of the Southern Hemisphere, influenza activity occurs typically during April–September. In temperate climate zones of the Northern and Southern Hemispheres, travelers also can be exposed to influenza during the summer, especially when traveling as part of large tourist groups (e.g., on cruise ships) that include persons from areas of the world in which influenza viruses are circulating (*470,471*). In the tropics, influenza occurs throughout the year. In a study among Swiss travelers to tropical and subtropical countries, influenza was the most frequently acquired vaccine-preventable disease (*472*).

Any traveler who wants to reduce the risk for influenza infection should consider influenza vaccination, preferably at least 2 weeks before departure. In particular, persons at high risk for complications of influenza and who were not vaccinated with influenza vaccine during the preceding fall or winter should consider receiving influenza vaccine before travel if they plan to travel:

- to the tropics,
- with organized tourist groups at any time of year, or
- to the Southern Hemisphere during April–September.

No information is available about the benefits of revaccinating persons before summer travel who already were vaccinated during the preceding fall, and revaccination is not recommended. Persons at high risk who receive the previous season's vaccine before travel should be receive the current vaccine the following fall or winter. Persons at higher risk for influenza complications should consult with their health-care practitioner to discuss the risk for influenza or other travel-related diseases before embarking on travel during the summer.

Recommended Vaccines for Different Age Groups

Each season, vaccination providers should check the latest information on FDA approval of the 2010–11 seasonal influenza vaccines and CDC recommendations for use of these vaccines to determine which vaccines are licensed for use in any particular age. Immunization providers should consult updated information on use of influenza vaccines from CDC (available at http://www.cdc.gov/flu) and FDA (available at http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/vaccinesafety/default.htm). The following information is based on approvals for the 2009–10 seasonal influenza vaccines.

When vaccinating children aged 6–35 months with TIV, health-care providers should use TIV that has been licensed by FDA for this age group (i.e., TIV manufactured by sanofi pasteur [FluZone] or CSL Biotherapies (Afluria) (*286*). TIV

from Novartis (Fluvirin) is FDA-approved in the United States for use among persons aged ≥4 years (*287*). One TIV preparation from GlaxoSmithKline (Fluarix) is licensed for use in children aged ≥3 years, and another preparation (FluLaval) is labeled for use in persons aged ≥18 years (*274,275,285*). LAIV from MedImmune (FluMist) is recommended for use by healthy nonpregnant persons aged 2–49 years (Table 2) (*360*). If a pediatric vaccine dose (0.25mL) is administered inadvertently to an adult, an additional pediatric dose (0.25 mL) should be given to provide a full adult dose (0.5mL). If the error is discovered later (after the patient has left the vaccination setting), an adult dose should be administered as soon as the patient can return. Vaccination with a formulation approved for adult use should be counted as a dose if inadvertently administered to a child.

An inactivated trivalent influenza vaccine (Fluzone High-Dose, sanofi pasteur.) that contains an increased amount of influenza virus antigen compared with other inactivated influenza vaccines was licensed in 2009. Fluzone High-Dose is available as single dose prefilled syringe formulation distinguished from Fluzone by a gray syringe plunger rod (*224*). As with other 2010–11 influenza vaccines, Fluzone High-Dose will contain the three recommended virus strains (A/California/7/2009 (H1N1)-like, A/Perth/16/2009 (H3N2)-like, and B/Brisbane/60/2008-like antigens) (*136*). ACIP recommends that all persons aged ≥65 years receive an inactivated 2010–11 seasonal influenza vaccination but has not expressed a preference for Fluzone High-Dose or any other inactivated influenza vaccine for use in persons aged ≥65 years (*473*). Whether or not the higher postvaccination immune responses observed among Fluzone High-Dose vaccine recipients (*221–223*) will result in greater protection against influenza illness is not known. High-dose vaccine should not be administered to persons aged <65 years. Several other new vaccine formulations are being evaluated in immunogenicity and efficacy trials; when licensed, these new products will increase the influenza vaccine supply and provide additional vaccine choices for practitioners and their patients. Providers should review the formulation and packaging before administering influenza vaccine to ensure the product used is appropriate for the age of the patient.

Influenza Vaccines and Use of Influenza Antiviral Medications

Administration of TIV to persons receiving influenza antivirals for treatment or chemoprophylaxis is acceptable. The effect on safety and effectiveness of LAIV coadministration with influenza antiviral medications has not been studied. However, because influenza antivirals reduce replication of influenza viruses, LAIV should not be administered until 48 hours after cessation of influenza antiviral therapy. If influenza antiviral medications are administered within 2 weeks after receipt of LAIV, the vaccine dose should be repeated 48 or more hours after the last dose of antiviral medication. Persons receiving antivirals within the period 2 days before to 14 days after vaccination with LAIV should be revaccinated at a later date with any approved vaccine formulation (*246,331*).

Considerations When Using LAIV

LAIV is an option for vaccination of healthy nonpregnant persons aged 2–49 years without contraindications, including HCP and other close contacts of high-risk persons (excepting severely immunocompromised hospitalized persons who require care in a protected environment). The precaution regarding use of LAIV in protected environments is based upon a theoretic concern that the live attenuated vaccine virus could be transmitted to severely immunocompromised persons. However, no transmission of LAIV in health-care settings ever has been reported, and because these viruses are also cold-adapted (and cannot effectively replicate at normal body temperature) the risk for transmitting a vaccine virus to a severely immunocompromised person and causing severe infection appears to be extremely low. HCP working in environments such as neonatal intensive care, oncology, or labor and delivery units can receive LAIV without any restrictions.

No preference is indicated for LAIV or TIV when considering vaccination of healthy nonpregnant persons aged 2–49 years. Possible advantages of LAIV include its potential to induce a broad mucosal and systemic immune response in children, its ease of administration, and the possibly increased acceptability of an intranasal rather than intramuscular route of administration.

If the vaccine recipient sneezes immediately after administration, the dose should not be repeated. However, if nasal congestion is present that might impede delivery of the vaccine to the nasopharyngeal mucosa, deferral of administration should be considered until resolution of the illness, or TIV should be administered instead. No data exist about concomitant use of nasal corticosteroids or other intranasal medications (*331*).

Although FDA licensure of LAIV excludes children aged 2–4 years with a history of asthma or recurrent wheezing, the precise risk, if any, of wheezing caused by LAIV among these children is unknown because experience with LAIV among these young children is limited. Young children might not have a history of recurrent wheezing if their exposure to respiratory viruses has been limited because of their age. Certain children might have a history of wheezing with respiratory illnesses but have not had asthma diagnosed.

Clinicians and vaccination programs should screen for asthma or wheezing illness (or history of wheezing illness) when considering use of LAIV for children aged 2–4 years, and should avoid use of this vaccine in children with asthma or a wheezing episode within the previous 12 months. Health-care providers should consult the medical record, when available, to identify children aged 2–4 years with asthma or recurrent wheezing that might indicate asthma. In addition, to identify children who might be at greater risk for asthma and possibly at increased risk for wheezing after receiving LAIV, parents or caregivers of children aged 2–4 years should be asked: "In the past 12 months, has a health-care provider ever told you that your child had wheezing or asthma?" Children whose parents or caregivers answer "yes" to this question and children who have asthma or who had a wheezing episode noted in the medical record during the preceding 12 months should not receive LAIV. TIV is available for use in children with asthma or wheezing (*474*). LAIV can be administered to persons with minor acute illnesses (e.g., diarrhea or mild upper respiratory tract infection with or without fever). However, if nasal congestion is present that might impede delivery of the vaccine to the nasopharyngeal mucosa, use of TIV, or deferral of administration should be considered until resolution of the illness, is recommended.LAIV is approved for use in persons aged 2–49 years. However, the effectiveness or safety of LAIV is not known or is of potential concern for certain persons, and LAIV is not recommended for these persons. Do not administer LAIV to the following groups:

- persons with a history of hypersensitivity, including anaphylaxis, to any of the components of LAIV or to eggs;
- children aged <2 years, because of an increased risk for hospitalization and wheezing observed in clinical trials;
- children aged 2–4 years whose parents or caregivers report that a health-care provider has told them during the preceding 12 months that their child had wheezing or asthma or whose medical record indicates a wheezing episode has occurred during the preceding 12 months;
- persons with asthma;
- persons aged ≥50 years;
- adults and children who have chronic pulmonary, cardiovascular (except isolated hypertension), renal, hepatic, neurologic/neuromuscular, hematologic, or metabolic disorders;
- adults and children who have immunosuppression (including immunosuppression caused by medications or by HIV);
- children or adolescents aged 6 months–18 years receiving aspirin or other salicylates (because of the association of Reye syndrome with wild-type influenza virus infection); or
- pregnant women.

A moderate or severe illness with or without fever is a precaution for use of LAIV. Development of GBS within 6 weeks following a previous dose of influenza vaccine is considered to be a precaution for use of influenza vaccines. LAIV should not be administered to close contacts of immunosuppressed persons who require a protected environment.

Personnel Who Can Administer LAIV

Low-level introduction of vaccine viruses into the environment probably is unavoidable when administering LAIV, but no instances have been reported of illness or attenuated vaccine virus infections among inadvertently exposed HCP or immunocompromised patients. The risk for acquiring vaccine viruses from the environment is unknown but is probably low; in addition, vaccine viruses are cold-adapted and attenuated, and unlikely to cause symptomatic influenza. Severely immunosuppressed persons should not administer LAIV. However, other persons at higher risk for influenza complications can administer LAIV. These include persons with underlying medical conditions placing them at higher risk or who are likely to be at risk, including pregnant women, persons with asthma, and persons aged ≥50 years.

Concurrent Administration of Influenza Vaccine With Other Vaccines

Use of LAIV concurrently with measles, mumps, rubella (MMR) alone and MMR and varicella vaccine among children aged 12–15 months has been studied, and no interference with the immunogenicity to antigens in any of the vaccines was observed (*331,475*). Among adults aged ≥50 years, the safety and immunogenicity of zoster vaccine and TIV was similar whether administered simultaneously or spaced 4 weeks apart (*476*). In the absence of specific data indicating interference, following ACIP's general recommendations for vaccination is prudent (*246*). Inactivated vaccines do not interfere with the immune response to other inactivated vaccines or to live vaccines. Inactivated or live vaccines can be administered simultaneously with LAIV. However, after administration of a live vaccine, at least 4 weeks should pass before another live vaccine is administered.

Recommendations for Vaccination Administration and Vaccination Programs

Influenza vaccination levels increased substantially over the past 20 years, and a record proportion of children received seasonal or pandemic influenza A (H1N1) vaccines in 2009–10. However, a majority of persons in most groups recommended for vaccination do not receive an annual vaccine. Strategies to improve vaccination levels, including using reminder/recall systems and standing orders programs (*408,409,423*), should be implemented whenever feasible. Vaccination efforts should begin as soon as vaccine is available and continue through the influenza season, which typically extends through April. Vaccination coverage can be increased by administering vaccine before and during the influenza season to persons during hospitalizations or routine health-care visits. Vaccinations can be provided in alternative settings (e.g., schools, pharmacies, grocery stores, workplaces, or other locations in the community), thereby making special visits to physicians' offices or clinics unnecessary. Coordinated campaigns such as the National Influenza Vaccination Week (December 6–12, 2010) provide opportunities to refocus public attention on the benefits, safety, and availability of influenza vaccination throughout the influenza season. The 2009 pandemic provided opportunities for innovative programs to administer vaccine in a variety of settings, and lessons learned from this experience should be applied when developing routine influenza immunization programs.

Discussing Risk for Adverse Events after Vaccination

Concern about vaccine safety is often cited by persons who refuse vaccination, including health-care workers. When educating patients about adverse events, clinicians should provide Vaccine Information Statements (available at http://www.cdc.gov/vaccines/pubs/vis), and emphasize the risks and benefits of vaccination. Providers should inform patients or parents that 1) TIV contains noninfectious killed viruses and cannot cause influenza; 2) LAIV contains weakened influenza viruses that cannot replicate outside the upper respiratory tract and are unlikely to infect others; 3) many patients will experience no side effects and most known side effects are mild, transient, and manageable, such as injection-site pain after receipt of TIV or rhinorrhea after LAIV; and 4) concomitant symptoms or respiratory disease unrelated to vaccination with either TIV or LAIV can occur after vaccination.

Patients concerned about more severe adverse events might be reassured by discussing the many safety studies available, the safety monitoring systems currently in use, and the immunization provider or program's previous experience with influenza vaccines. Providers concerned about the risk for severe adverse events or who observe or report a severe adverse event after vaccination should keep in mind that relatively common events will occur by chance after vaccination. For example, one study used the background rate of spontaneous abortion to estimate that 397 per 1 million vaccinated pregnant women would be predicted to have a spontaneous abortion within 1 day of vaccination (*477*). Even rare events will be observed by chance after vaccination if large numbers of persons are vaccinated, as occurs with annual influenza immunization campaigns. For example, if a cohort of 10 million individuals was vaccinated, approximately 22 cases of GBS and six cases of sudden death would be expected to occur within 6 weeks of vaccination as coincident background cases unrelated to vaccination (*477*).

Information About the Vaccines for Children Program

The Vaccines for Children (VFC) program supplies vaccine to all states, territories, and the District of Columbia for use by participating providers. These vaccines are to be provided to eligible children without vaccine cost to the patient or the provider. Although the provider might charge a vaccine administration fee, vaccination will not be denied to parents who cannot pay an administration fee. All routine childhood vaccines recommended by ACIP are available through this program, including influenza vaccines. The program saves parents and providers out-of-pocket expenses for vaccine purchases and provides cost savings to states through CDC's vaccine contracts. The program results in lower vaccine prices and ensures that all states pay the same contract prices. Detailed information about the VFC program is available at http://www.cdc.gov/vaccines/programs/vfc/default.htm.

Influenza Vaccine Supply Considerations

The annual supply of influenza vaccine and the timing of its distribution cannot be guaranteed in any year. During the 2009–10 influenza season, 114 million doses of seasonal influenza vaccine were distributed in the United States. However, influenza vaccine distribution delays or vaccine shortages remain possible. One factor that affects production is the inherent critical time constraints in manufacturing the vaccine given the annual updating of the influenza vaccine strains. Multiple manufacturing and regulatory issues also might affect the production schedule.

If supplies of seasonal influenza vaccine are not adequate, vaccination should be carried out in accordance with local circumstances of supply and demand based on the judgment of state and local health officials and health-care providers. National guidance for tiered use of influenza vaccine during prolonged distribution delays or supply shortfalls will be based primarily on epidemiologic studies indicating that certain persons are at higher risk for influenza infection or influenza-related complications, as well as which vaccine formulations have limited supplies. When epidemiologic studies or other data that would guide tiered use are unavailable, persons previously demonstrated to be at higher risk for influenza or influenza-related complications should be among those targeted by immunization programs for receipt of limited supplies. Even if vaccine use is not restricted to certain persons known to be at higher risk for influenza complications, strategies employed by immunization programs and providers during periods of limited vaccine availability should emphasize outreach to persons at higher risk for influenza or influenza-related complications (Box), or who are part of populations that have limited access to medical care. During shortages of TIV, LAIV should be used preferentially when feasible for all healthy nonpregnant persons aged 2–49 years (including HCP) who desire or are recommended for vaccination to increase the availability of inactivated vaccine for persons at high risk.

Timing of Vaccination

Vaccination efforts should be structured to ensure the vaccination of as many persons as possible over the course of several months, with emphasis on vaccinating before influenza activity in the community begins. Even if vaccine distribution begins before October, distribution probably will not be completed until December or January. The following recommendations reflect this phased distribution of vaccine.

In any given year, the optimal time to vaccinate patients cannot be determined precisely because influenza seasons vary in their timing and duration, and more than one outbreak might occur in a single community in a single year. In the United States, localized outbreaks that indicate the start of seasonal influenza activity can occur as early as October. However, in >80% of influenza seasons since 1976, peak influenza activity (which often is close to the midpoint of influenza activity for the season) has not occurred until January or later, and in >60% of seasons, the peak was in February or later. In general, health-care providers should begin offering vaccination soon after vaccine becomes available and if possible by October. To avoid missed opportunities for vaccination, providers should offer vaccination during routine health-care visits or during hospitalizations whenever vaccine is available.

Vaccination efforts should continue throughout the season, because the duration of the influenza season varies and influenza might not appear in certain communities until February or March. Providers should offer influenza vaccine routinely, and organized vaccination campaigns should continue throughout the influenza season, including after influenza activity has begun in the community. Vaccine administered in December or later, even if influenza activity has already begun, is likely to be beneficial in the majority of influenza seasons. The majority of adults have antibody protection against influenza virus infection within 2 weeks after vaccination (*478,479*).

All children aged 6 months–8 years who are recommended for 2 doses should receive their first dose as soon after vaccine becomes available as is feasible and should receive the second dose ≥4 weeks later. This practice increases the opportunity for both doses to be administered before or shortly after the onset of influenza activity.

Planners are encouraged to develop the capacity and flexibility to schedule at least one vaccination clinic in December. Guidelines for planning large-scale vaccination clinics, including school-based clinics, are available at http://www.cdc.gov/flu/professionals/vaccination/vax_clinic.htm, http://www.cdc.gov/h1n1flu/vaccination/statelocal/settingupclinics.htm, and http://www.cdc.gov/h1n1flu/vaccination/slv.

During a vaccine shortage or delay, substantial proportions of TIV or LAIV doses might not be released and distributed until November and December or later. When the vaccines are substantially delayed or disease activity has not subsided, providers should consider offering vaccination clinics into January and beyond as long as vaccine supplies are available.

Strategies for Implementing Vaccination Recommendations

The expansion of the recommendations to all persons aged ≥6 months highlights the importance of making influenza vaccine readily accessible in a variety of settings. Many of the persons at highest risk for complications will likely continue to be vaccinated in health-care settings. However, vaccination in health-care settings must increasingly be complemented by vaccination in nonmedical settings that increase convenience and access. During the 2009–2010 H1N1 Vaccination Program, substantial efforts were made at the state and local level to direct vaccine to locations such as schools, pharmacies, workplaces, and health departments.

Health-Care Settings

Health-care settings remain a central component of an overall influenza vaccination strategy. Studies consistently show that provider recommendation is the strongest predictor of

vaccination (*425,480,481*). While nonmedical settings play an important role for those motivated to seek vaccination, health-care settings are critical for facilitating vaccination of all those who come into contact with the setting, including those who might not seek out vaccination.

Successful vaccination programs combine publicity and education for HCP and other potential vaccine recipients, use of reminder/recall systems, assessment of practice-level vaccination rates with feedback to staff, and efforts to remove administrative and financial barriers that prevent persons from receiving the vaccine, including use of standing orders programs (*409,482,483*). The use of standing orders programs by long-term–care facilities (e.g., nursing homes and skilled nursing facilities), hospitals, and home health agencies ensures that vaccination is offered. Standing orders programs for influenza vaccination should be conducted under the supervision of a licensed practitioner according to a physician-approved facility or agency policy by HCP trained to screen patients for contraindications to vaccination, administer vaccine, and monitor and report adverse events. The Centers for Medicare and Medicaid Services (CMS) has removed the physician signature requirement for the administration of influenza and pneumococcal vaccines to Medicare and Medicaid patients in hospitals, long-term–care facilities, and home health agencies (*484*). To the extent allowed by local and state law, these facilities and agencies can implement standing orders for influenza and pneumococcal vaccination of Medicare- and Medicaid-eligible patients. Payment for influenza vaccine under Medicare Part B is available (*485,486*). Other settings (e.g., outpatient facilities, managed-care organizations, assisted living facilities, correctional facilities, pharmacies, and adult workplaces) are encouraged to introduce standing orders programs (*487*). In addition, physician reminders (e.g., flagging charts) and patient reminders are recognized strategies for increasing rates of influenza vaccination (*483*).

Outpatient Facilities Providing Ongoing Care

Staff in facilities providing ongoing medical care (e.g., physicians' offices, public health clinics, employee health clinics, hemodialysis centers, hospital specialty-care clinics, and outpatient rehabilitation programs) should offer vaccine to all patients during visits throughout the influenza season. The offer of vaccination and its receipt or refusal should be documented in the medical record or immunization information system. Patients who do not have regularly scheduled visits during the fall should be reminded by mail, telephone, or other means of the need for vaccination.

Outpatient Facilities Providing Episodic or Acute Care

Acute health-care facilities (e.g., EDs and walk-in clinics) should offer vaccinations throughout the influenza season or provide written information regarding why, where, and how to obtain the vaccine. This written information should be provided in languages at literacy levels appropriate for the populations served by the facility.

Acute-Care Hospitals

Hospitals should serve as a key setting for identifying persons at increased risk for influenza complications. Unvaccinated persons without contraindications who are hospitalized at any time during the period when vaccine is available should be offered and strongly encouraged to receive influenza vaccine before they are discharged. Standing orders to offer influenza vaccination to all hospitalized persons should be considered.

Nursing Homes and Other Long-Term–Care Facilities

Vaccination should be provided routinely to all residents of long-term–care facilities. If possible, all residents should be vaccinated before influenza season. In the majority of seasons, TIV will become available to long-term–care facilities in October or November, and vaccination should commence as soon as vaccine is available. As soon as possible after admission to the facility, the benefits and risks of vaccination should be discussed and education materials provided (*488*). Informed consent is required, but this does not necessarily mean a signed consent must be present in order to implement a standing order for vaccination (*489*). Residents admitted after completion of the vaccination program at the facility should be vaccinated at the time of admission.

Lower rates of severe illness among older persons were observed during the 2009 pandemic, but outbreaks among residents of nursing homes and other long-term–care facilities still occurred (*490*). Although the influenza viruses that will circulate during the 2010–11 season are unknown, multiple influenza types and subtypes that often infect and cause severe infections among older adults (e.g., H3N2) circulate each winter influenza season. The 2010–11 influenza vaccine formulation should be administered to all residents and staff.

Since October 2005, CMS has required nursing homes participating in the Medicare and Medicaid programs to offer all residents influenza and pneumococcal vaccines and to document the results. According to the requirements, each resident is to be vaccinated unless contraindicated medically, the resident or a legal representative refuses vaccination, or the vaccine is not available because of shortage. This information is

to be reported as part of the CMS Minimum Data Set, which tracks nursing home health parameters (*486,491*).

Vaccination Provided by Visiting Nurses and Others Providing Home Care to Persons at High Risk

Vaccine should be administered in the home if necessary as soon as influenza vaccine is available and throughout the influenza season. Caregivers and other persons in the household (including children) should be referred for vaccination.

Vaccination for Health-Care Personnel

Health-care facilities should offer influenza vaccinations to all HCP, including night, weekend, and temporary staff. Particular emphasis should be placed on providing vaccinations to workers who provide direct care for persons at high risk for influenza complications. Efforts should be made to educate HCP regarding the benefits of vaccination and the potential health consequences of influenza illness for their patients, themselves, and their family members. All HCP should be provided convenient access to influenza vaccine at the work site, free of charge, as part of employee health programs (*437,455,462*).

Other Settings

Influenza vaccination has increasingly become available in nonmedical settings. In the 2009–2010 vaccination season, 33% of seasonal influenza vaccinations occurred in health departments, pharmacies or drug stores, workplaces, schools, or other nonmedical locations (CDC, unpublished data, 2009). The proportion of 2009 H1N1 vaccine administered in these settings was 45% (CDC, unpublished data, 2010). Availability of vaccine in a range of settings such as pharmacies and the workplace is especially important for persons who do not regularly accesss the health-care system. In addition, with the recent expansion of the influenza recommendations to include all persons aged ≥6 months, implementation of strategies that are sustainable beyond vaccination in provider offices are necessary. School-located vaccination provides an opportunity to address the challenges associated with large numbers of children to vaccinate, a short window of time for vaccination, and the need for annual revaccination. A number of states and immunization programs have effectively conducted school-located vaccination both for seasonal vaccination (*492,493*) and 2009 H1N1 vaccination (*494*). School-located vaccination does, however, present challenges from a resource perspective both for vaccine costs and program costs (*493*), because reimbursement practices might be different compared with those used in medical settings. In addition, documentation of vaccination must be provided to the vaccinated person's primary care provider and where appropriate state or local vaccine registries.

Nonmedical settings that should be considered to reach the elderly include assisted living housing, retirement communities, and recreation centers. Such facilities should offer unvaccinated residents, attendees, and staff annual on-site vaccination before the start of the influenza season. Continuing to offer vaccination throughout the fall and winter months is appropriate. Efforts to vaccinate newly admitted patients or new employees also should be continued, both to prevent illness and to avoid having these persons serve as a source of new influenza infections. Staff education should emphasize the benefits for self, staff and patients of protection from influenza through vaccination.

Future Directions for Research and Recommendations Related to Influenza Vaccine

Although available influenza vaccines are effective and safe, additional research is needed to improve prevention efforts. Most severe morbidity and mortality during typical influenza seasons occurs among persons aged ≥65 years of those who have chronic medical conditions (*6,7,24*). More immunogenic influenza vaccines are needed for persons at higher risk for influenza-related complications. Additional research also is needed to understand potential biases in estimating the benefits of vaccination among older adults in reducing hospitalizations and deaths (*134,241,495*). Additional studies of the relative cost-effectiveness and cost utility of influenza vaccination among children and adults, especially those aged <65 years, are needed and should be designed to account for year-to-year variations in influenza attack rates, illness severity, hospitalization costs and rates, and vaccine effectiveness when evaluating the long-term costs and benefits of annual vaccination (*496*). Additional data on indirect effects of vaccination also are needed to quantify the benefits of influenza vaccination of HCP in protecting their patients (*379*) and the impact of a universal vaccination recommendation on influenza epidemiology, particularly the impact on persons at higher risk for influenza complications. In addition, a better understanding is needed of how to motivate persons, particularly those at risk for influenza-related complications and their close contacts, to seek or accept annual influenza vaccination.

The expansion of annual vaccination recommendations to include all persons aged ≥6 months will require a substantial increase in resources for epidemiologic research to develop long-term studies capable of assessing the possible effects on community-level transmission. In Canada, a universal vac-

cination recommendation implemented in Ontario in 2000 has been compared with typical practice in other Canadian provinces. These studies have been challenging to conduct, but have indicated that a universal recommendation for annual vaccination is associated with overall reductions in influenza-related mortality, hospitalizations, ED use, physicians' office visits, and antibiotic use (*388,389,396*). However, differences between health-care systems in Canada and the United States limit the ability to generalize the findings in Ontario to the United States, and measures of the impact of a universal recommendation in the United States will likely require many years to evaluate. Additional planning to improve surveillance systems capable of monitoring effectiveness, safety and vaccine coverage, and further development of implementation strategies will be necessary. Vaccination programs capable of delivering annual influenza vaccination to a broad range of the population could potentially serve as a resilient and sustainable platform for delivering vaccines and monitoring outcomes for other urgently required public health interventions (e.g., vaccines for future influenza pandemics or medical countermeasures to prevent or treat illnesses caused by acts of terrorism).

Seasonal Influenza Vaccine and Influenza Viruses of Animal Origin

Human infection with novel or nonhuman influenza A virus strains, including influenza A viruses of animal origin, is a nationally notifiable disease in the United States (*497*). Human infections with nonhuman or novel human influenza A virus should be identified quickly and investigated to determine possible sources of exposure, identify additional cases, and evaluate the possibility of human-to-human transmission because transmission patterns could change over time with variations in these influenza A viruses.

Sporadic severe and fatal human cases of infection with highly pathogenic avian influenza A (H5N1) virus have been identified in Asia, Africa, Europe, and the Middle East, primarily among persons who have had direct or close unprotected contact with sick or dead birds associated with the ongoing H5N1 panzootic among birds (*498–506*). Severe lower respiratory illness with multiorgan failure has been reported in fatal H5N1 cases, and asymptomatic infection and clinically mild cases also have been reported (*507–510*). Limited, nonsustained human-to-human transmission of H5N1 virus has likely occurred in some case clusters (*508,511*). To date, there is no evidence of genetic reassortment between human influenza A and H5N1 viruses. However, influenza viruses derived from strains circulating among poultry (e.g., the H5N1 virus, which has caused outbreaks of avian influenza and occasionally have infected humans) have the potential to recombine with human influenza A viruses (*512,513*). To date, highly pathogenic H5N1 virus has not been identified in wild or domestic birds or in humans in the United States. Guidance for testing suspected cases of H5N1 virus infection among persons in the United States and follow-up of contacts is available (*514,515*). Human H5N1 cases have continued to occur in 2009 and 2010, including in the Middle East and Southeast Asia (*516*).

Human illness from infection with different avian influenza A subtype viruses also has been documented, including infections with low pathogenic and highly pathogenic viruses. A range of clinical illness has been reported for human infection with low pathogenic avian influenza viruses, including conjunctivitis with influenza A (H7N7) virus in the United Kingdom, lower respiratory tract disease and conjunctivitis with influenza A (H7N2) virus in the United Kingdom, and uncomplicated ILI with influenza A (H9N2) virus in Hong Kong and China (*517–523*). Two human cases of infection with low pathogenic influenza A (H7N2) have been reported in the United States (*520*). Although human infections with highly pathogenic A (H7N7) virus infections typically have ILI or conjunctivitis, severe infections, including one fatal case in the Netherlands, have been reported following exposure to poultry (*524–526*). Conjunctivitis also has been reported because of human infection with highly pathogenic influenza A (H7N3) virus in Canada and low pathogenic A (H7N3) in the United Kingdom (*517,525*). In contrast, sporadic infections with highly pathogenic avian influenza A (H5N1) virus have caused severe illness in many countries, with an overall case-fatality proportion of approximately 60% (*508,526*).

Swine influenza A (H1N1), A (H1N2), and A (H3N2) viruses, including reassortant viruses, are endemic among pig populations in the United States (*527*). Two clusters of influenza A (H2N3) virus infections among pigs have been reported recently (*528*). Outbreaks among pigs normally occur in colder weather months (late fall and winter) and sometimes with the introduction of new pigs into susceptible herds. An estimated 30% of the pig population in the United States has serologic evidence of having had swine influenza A (H1N1) virus infection. Sporadic human infections with a variety of swine influenza A viruses occur in the United States, but the incidence of these human infections is unknown (*529–534*). Persons infected with swine influenza A viruses typically report direct contact with ill pigs or places where pigs have been present (e.g., agricultural fairs or farms) and have symptoms that are clinically indistinguishable from infection with other respiratory viruses (*531,532,535,536*). Swine influenza virus infection has not been associated with household exposure to pork products or consumption of pork. Clinicians should consider

swine influenza A virus infection in the differential diagnosis of patients with ILI who have had recent contact with pigs. Sporadic cases among persons whose infections were linked to swine exposure have not resulted in sustained human-to-human transmission of swine influenza A viruses or community outbreaks (*9,536*). The 2009 pandemic influenza A (H1N1) virus contains some genes previously found in viruses currently circulating among swine, but the origin of the pandemic has not been definitively linked to swine exposures among humans. Although immunity to swine influenza A viruses appears to be low (<2%) in the overall human population, 10%–20% of persons with occupational exposure to pigs (e.g., pig farmers or pig veterinarians) have been documented in certain studies to have antibody evidence of prior swine influenza A (H1N1) virus infection (*529,537*).

Current seasonal influenza vaccines are not expected to provide protection against human infection with avian influenza A viruses, including influenza A (H5N1) viruses, or to provide protection against influenza A viruses currently circulating exclusively in swine (*318,448*). However, reducing seasonal influenza risk through influenza vaccination of persons who might be exposed to nonhuman influenza viruses (e.g., H5N1 virus) might reduce the theoretic risk for recombination of influenza A viruses of animal origin and human influenza A viruses by preventing seasonal influenza A virus infection within a human host.

CDC has recommended that persons who are charged with responding to avian influenza outbreaks among poultry receive seasonal influenza vaccination (*538,539*). As part of preparedness activities, the Occupational Safety and Health Administration (OSHA) has issued an advisory notice regarding poultry worker safety that is intended for implementation in the event of a suspected or confirmed avian influenza outbreak at a poultry facility in the United States. OSHA guidelines recommend that poultry workers in an involved facility receive vaccination against seasonal influenza; OSHA also has recommended that HCP involved in the care of patients with documented or suspected avian influenza should be vaccinated with the most recent seasonal human influenza vaccine to reduce the risk for co-infection with human influenza A viruses (*539*).

Recommendations for Using Antiviral Agents

Annual vaccination is the primary strategy for preventing complications of influenza virus infections. Antiviral medications with activity against influenza viruses are useful adjuncts in the prevention of influenza, and effective when used early in the course of illness for treatment. Four influenza antiviral agents are licensed in the United States: amantadine, rimantadine, zanamivir, and oseltamivir. Investigational antiviral medications, such as peramivir and intravenous formulations of zanamivir, might be available under investigational new drug protocols (*540*).

During the 2007–08 influenza season, influenza A (H1N1) viruses with a mutation that confers resistance to oseltamivir became more common in the United States and other countries (*541–543*). As of June 2010, in the United States, approximately 99% of seasonal influenza A (H1N1) viruses (i.e., H1N1 viruses not associated with the 2009 pandemic) tested have been resistant to oseltamivir. None of the influenza A (H3N2) or influenza B viruses tested were resistant to oseltamivir. However, few seasonal influenza viruses isolated after May 2009 are available for testing. As of June 2010, with few exceptions, 2009 pandemic influenza A (H1N1) virus strains that began circulating in April 2009 remained sensitive to oseltamivir, and all were sensitive to zanamivir (*16*). Sporadic cases of 2009 pandemic influenza A (H1N1) virus infection with an H275Y mutation in neuraminidase associated with oseltamivir resistance have been reported worldwide, but as of June 2010, no sustained community-wide transmission has been identified (*544*). Such oseltamivir-resistant virus infections have been identified in severely immunosuppressed patients, persons receiving oseltamivir chemoprophylaxis, and in some persons without oseltamivir exposure, including some influenza illness clusters (*544–549*). CDC's recommendations for use of influenza antiviral medications should be consulted for guidance on antiviral use (*15*). New guidance on clinical management of influenza, including use of antivirals, also is available from the Infectious Diseases Society of America and the World Health Organization (*550–552*). ACIP recommendations for antiviral use will be published separately later in 2010.

Sources of Information Regarding Influenza and its Surveillance

Information regarding influenza surveillance, prevention, detection, and control is available at http://www.cdc.gov/flu. During October–May, surveillance information is updated weekly. In addition, periodic updates regarding influenza are published in *MMWR* (http://www.cdc.gov/mmwr). Additional information regarding influenza vaccine can be obtained by calling 1-800-CDC-INFO (1-800-232-4636). State and local health departments should be consulted about availability of influenza vaccine, access to vaccination programs, information related to state or local influenza activity, reporting of influenza outbreaks and influenza-related pediatric deaths, and advice concerning outbreak control.

Vaccine Adverse Event Reporting System (VAERS)

Clinically significant adverse events that follow vaccination should be reported to the Vaccine Adverse Event Reporting System (VAERS) at http://vaers.hhs.gov/esub/index. Reports can be filed securely online, by mail, or by fax. A VAERS form can be downloaded from the VAERS website or requested by sending an e-mail message to info@vaers.org, by calling telephone 1-800-822-7967, or by sending a faxed request to 1-877-721-0366. Additional information on VAERS or vaccine safety is available at http://vaers.hhs.gov/about/index or by calling telephone 1-800-822-7967.

Reporting of Adverse Events that Occur After Administering Antiviral Medications (MedWatch)

Health-care professionals should report all serious adverse events (SAEs) after antiviral medication use promptly to MedWatch, FDA's adverse event reporting program for medications. SAEs are defined as medical events that involve hospitalization, death, life-threatening illness, disability, or certain other medically important conditions. SAEs that follow administration of medications should be reported at http://www.fda.gov/medwatch/report/hcp.htm.

National Vaccine Injury Compensation Program

The National Vaccine Injury Compensation Program (VICP), established by the National Childhood Vaccine Injury Act of 1986, as amended, provides a mechanism through which compensation can be paid on behalf of a person determined to have been injured or to have died as a result of receiving a vaccine covered by VICP. The Vaccine Injury Table lists the vaccines covered by VICP and the injuries and conditions (including death) for which compensation might be paid. If the injury or condition is not on the Table, or does not occur within the specified time period on the Table, persons must prove that the vaccine caused the injury or condition.

For a person to be eligible for compensation, the general filing deadlines for injuries require claims to be filed within 3 years after the first symptom of the vaccine injury; for a death, claims must be filed within 2 years of the vaccine-related death and not more than 4 years after the start of the first symptom of the vaccine-related injury from which the death occurred. When a new vaccine is covered by VICP or when a new injury/condition is added to the Table, claims that do not meet the general filing deadlines must be filed within 2 years from the date the vaccine or injury/condition is added to the Table for injuries or deaths that occurred up to 8 years before the Table change. Persons of all ages who receive a VICP-covered vaccine might be eligible to file a claim. Both the intranasal (LAIV) and injectable (TIV) trivalent influenza vaccines are covered under VICP. Additional information about VICP is available at http//www.hrsa.gov/vaccinecompensation or by calling 1-800-338-2382.

Additional Information Regarding Influenza Virus Infection Control Among Specific Populations

Each year, ACIP provides general, annually updated information regarding control and prevention of influenza. Other reports related to controlling and preventing influenza among specific populations (e.g., immunocompromised persons, HCP, hospital patients, pregnant women, children, and travelers) also are available in the following publications:

- CDC. General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Family Physicians (AAFP). MMWR 2006;55(No. RR-15).
- CDC. Influenza vaccination of health-care personnel: recommendations of the Healthcare Infection Control Practices Advisory Committee (HICPAC) and the Advisory Committee on Immunization Practices (ACIP). MMWR 2006;55(No. RR-2).
- CDC. Recommended immunization schedules for persons aged 0 through 18 years—United States, 2010. MMWR 2010;58:Q1–4.
- CDC. Guidelines for preventing health-care–associated pneumonia, 2003: recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee. MMWR 2004;53(No. RR-3).
- CDC. Respiratory hygiene/cough etiquette in health-care settings. Atlanta, GA: US Department of Health and Human Services, CDC; 2003. Available at http://www.cdc.gov/flu/professionals/infectioncontrol/resphygiene.htm.
- CDC. Prevention and control of vaccine-preventable diseases in long-term–care facilities. Atlanta, GA: US Department of Health and Human Services, CDC; 2006. Available at http://www.cdc.gov/flu/professionals/infectioncontrol/longtermcare.htm.
- CDC. Vaccine safety. Atlanta, GA: US Department of Health and Human Services, CDC; 2009. Available at http://www.cdc.gov/vaccinesafety/index.htm.

- American College of Obstetricians and Gynecologists. Influenza vaccination and treatment during pregnancy. ACOG committee opinion no. 305. Obstet Gynecol 2004;104:1125–6.
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ACIP Provisional Recommendations for Measles-Mumps-Rubella (MMR) 'Evidence of Immunity' Requirements for Healthcare Personnel

Date of ACIP vote: June 24, 2009
Date of posting of provisional recommendations: August 28, 2009

On June 24, 2009 the ACIP voted on revised recommendations for measles-mumps-rubella (MMR) 'evidence of immunity' requirements for healthcare personnel*. The Healthcare Infection Control Practices Advisory Committee (HICPAC) has endorsed these changes.

Summary of new recommendations:

Adequate presumptive evidence of immunity to measles, rubella, and mumps for persons who work in health care facilities:

Measles:
a. Documented administration of two doses of live measles virus vaccine[1] *or*
b. Laboratory evidence of immunity or laboratory confirmation of disease *or*
c. Born before 1957[2 3 4]

Rubella
a. Documented administration of one dose of live rubella virus vaccine[1] *or*
b. Laboratory evidence of immunity or laboratory confirmation of disease *or*
c. Born before 1957 (except women of childbearing age who could become pregnant)[2 3 4]

Mumps
a. Documented administration of two doses of live mumps virus vaccine[1] *or*
b. Laboratory evidence of immunity or laboratory confirmation of disease *or*
c. Born before 1957[2 3 4]

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[1] The first dose should be administered on or after the first birthday; the second dose of measles and mumps-containing vaccine should be administered no earlier than one month (i.e., a minimum of 28 days) after the first dose. Combined MMR vaccine generally should be used whenever any of its component vaccines is indicated.

[2] May vary depending on current state or local requirements.

[3] For unvaccinated personnel born before 1957 who lack laboratory evidence of measles, mumps and/or rubella immunity or laboratory confirmation of disease, healthcare facilities should consider vaccinating personnel with two doses of MMR vaccine at the appropriate interval (for measles and mumps) and one dose of MMR vaccine (for rubella), respectively.

[4] For unvaccinated personnel born before 1957 who lack laboratory evidence of measles, mumps and/or rubella immunity or laboratory confirmation of disease, healthcare facilities should recommend two doses of MMR vaccine during an outbreak of measles or mumps and one dose during an outbreak of rubella.

* These recommendations update two previous ACIP documents:
1. Immunization of Health Care Workers: Recommendations of the Advisory Committee on Immunization Practices (ACIP) and the Hospital Infection Control Practices Advisory Committee (HICPAC). Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/00050577.htm
2. Measles, Mumps, and Rubella----Vaccine Use and Strategies for Elimination of Measles, Rubella, and Congenital Rubella Syndrome and the Control of Mumps: Recommendations of the Advisory Committee on Immunization Practices. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/00053391.htm.

This document available at:
http://www.cdc.gov/vaccines/recs/provisional/downloads/mmr-evidence-immunity-Aug2009-508.pdf

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Use of Combination Measles, Mumps, Rubella, and Varicella Vaccine

Recommendations of the Advisory Committee on Immunization Practices

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

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Use of Combination Measles, Mumps, Rubella, and Varicella Vaccine

Recommendations of the Advisory Committee on Immunization Practices (ACIP)

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Summary

This report presents new recommendations adopted in June 2009 by CDC's Advisory Committee on Immunization Practices (ACIP) regarding use of the combination measles, mumps, rubella, and varicella vaccine (MMRV, ProQuad, Merck & Co., Inc.). MMRV vaccine was licensed in the United States in September 2005 and may be used instead of measles, mumps, rubella vaccine (MMR, M-M-RII, Merck & Co., Inc.) and varicella vaccine (VARIVAX, Merck & Co., Inc.) to implement the recommended 2-dose vaccine schedule for prevention of measles, mumps, rubella, and varicella among children aged 12 months–12 years. At the time of its licensure, use of MMRV vaccine was preferred for both the first and second doses over separate injections of equivalent component vaccines (MMR vaccine and varicella vaccine), which was consistent with ACIP's 2006 general recommendations on use of combination vaccines (CDC. General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices [ACIP]. MMWR 2006;55;[No. RR-15]). Since July 2007, supplies of MMRV vaccine have been temporarily unavailable as a result of manufacturing constraints unrelated to efficacy or safety. MMRV vaccine is expected to be available again in the United States in May 2010.

In February 2008, on the basis of preliminary data from two studies conducted postlicensure that suggested an increased risk for febrile seizures 5–12 days after vaccination among children aged 12–23 months who had received the first dose of MMRV vaccine compared with children the same age who had received the first dose of MMR vaccine and varicella vaccine administered as separate injections at the same visit, ACIP issued updated recommendations regarding MMRV vaccine use (CDC. Update: recommendations from the Advisory Committee on Immunization Practices [ACIP] regarding administration of combination MMRV vaccine. MMWR 2008;57:258–60). These updated recommendations expressed no preference for use of MMRV vaccine over separate injections of equivalent component vaccines for both the first and second doses.

The final results of the two postlicensure studies indicated that among children aged 12–23 months, one additional febrile seizure occurred 5–12 days after vaccination per 2,300–2,600 children who had received the first dose of MMRV vaccine compared with children who had received the first dose of MMR vaccine and varicella vaccine administered as separate injections at the same visit. Data from postlicensure studies do not suggest that children aged 4–6 years who received the second dose of MMRV vaccine had an increased risk for febrile seizures after vaccination compared with children the same age who received MMR vaccine and varicella vaccine administered as separate injections at the same visit.

In June 2009, after consideration of the postlicensure data and other evidence, ACIP adopted new recommendations regarding use of MMRV vaccine for the first and second doses and identified a personal or family (i.e., sibling or parent) history of seizure as a precaution for use of MMRV vaccine. For the first dose of measles, mumps, rubella, and varicella vaccines at age 12–47 months, either MMR vaccine and varicella vaccine or MMRV vaccine may be used. Providers who are considering administering MMRV vaccine should discuss the benefits and risks of both vaccination options with the parents or caregivers. Unless the parent or caregiver expresses a preference for MMRV vaccine, CDC recommends that MMR vaccine and varicella vaccine should be administered for the first dose in this age group. For

The material in this report originated in the National Center for Immunization and Respiratory Diseases, Anne Schuchat, MD, Director, and the Division of Viral Diseases, Larry Anderson, MD, Director; and the National Center for Emerging and Zoonotic Infectious Diseases (proposed), Thomas Hearn, PhD, Acting Director, and the Division of Healthcare Quality Promotion, Denise Cardo, MD, Director.

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the second dose of measles, mumps, rubella, and varicella vaccines at any age (15 months–12 years) and for the first dose at age ≥48 months, use of MMRV vaccine generally is preferred over separate injections of its equivalent component vaccines (i.e., MMR vaccine and varicella vaccine). This recommendation is consistent with ACIP's 2009 provisional general recommendations regarding use of combination vaccines (available at http://www.cdc.gov/vaccines/recs/provisional/downloads/combo-vax-Aug2009-508.pdf), which state that use of a combination vaccine generally is preferred over its equivalent component vaccines.

Introduction

To prevent measles, mumps, rubella, and varicella, the Advisory Committee on Immunization Practices (ACIP) recommends a 2-dose vaccine schedule in childhood, with the first dose administered at age 12–15 months and the second dose at age 4–6 years (*1,2*). In September 2005, the combination quadrivalent measles, mumps, rubella, and varicella vaccine (MMRV, ProQuad, Merck & Co., Inc.) was licensed by the Food and Drug Administration for use among children aged 12 months–12 years, and indications for its use were published subsequently (*3*). The availability of MMRV vaccine meant that two vaccination options were available to implement the ACIP recommendation for vaccination of children aged 12 months–12 years: 1) trivalent measles, mumps, rubella vaccine (MMR, M-M-RII, Merck & Co., Inc.) and monovalent varicella vaccine (VARIVAX, Merck & Co., Inc.) administered as two separate injections or 2) combination MMRV vaccine administered as one injection. Consistent with ACIP's 2006 general recommendations on immunization, use of the combination MMRV vaccine was preferred over separate injections of equivalent component vaccines (MMR vaccine and varicella vaccine) (*2,3*). Since July 2007, supplies of MMRV vaccine have been temporarily unavailable as a result of manufacturing constraints unrelated to efficacy or safety (i.e., lower-than-expected yields of bulk varicella-zoster virus in production lots) (*4,5*). MMRV vaccine is expected to be available again in the United States in May 2010.

The two vaccination options are considered to provide the same protection against the four diseases. In MMRV vaccine prelicensure studies conducted among children aged 12–23 months, fever and rash had been reported at a greater rate 0–42 days following vaccination among children who received a first dose of MMRV vaccine (n = 4,497) than among children who received first doses of MMR vaccine and varicella vaccine (n = 2,038) (*6*). In light of these findings, to evaluate if an increased risk for febrile seizures might be associated with the first dose of MMRV vaccine, CDC and Merck initiated separate postlicensure studies. Preliminary data from these two studies presented to ACIP in February 2008 suggested a 2.3-times higher risk for febrile seizures among children aged 12–23 months during the 5–12 or 7–10 days after administration of the first dose of MMRV vaccine compared with administration of the first dose of MMR vaccine and varicella vaccine at the same time (*7*). On the basis of these preliminary data, in February 2008, ACIP issued updated recommendations expressing no preference for use of MMRV vaccine over separate injections of equivalent component vaccines (i.e., MMR vaccine and varicella vaccine) for both the first and second dose (*7*). ACIP also established a workgroup to evaluate postlicensure and other safety data regarding the risk for febrile seizures after MMRV vaccine and formulate policy options for use of MMRV vaccine for consideration by ACIP.

In June 2009, after consideration of final data from the postlicensure studies and other evidence, ACIP adopted new recommendations regarding use of MMRV vaccine. This report provides these recommendations and replaces the 2008 recommendations for the use of MMRV vaccine (*7*).

Methods

The ACIP MMRV Vaccine Safety Workgroup was formed in spring 2008 and included federal and nonfederal experts from diverse backgrounds, including vaccine safety; epidemiology and vaccines related to measles, mumps, rubella, and varicella; statistics and pharmacoepidemiology; clinical pediatric neurology, infectious diseases, and primary care; and vaccinology and vaccine policy. The workgroup also sought input from partner organizations (e.g., the American Academy of Pediatrics and the American Academy of Family Physicians) and from local and state health departments. In addition, members of the CDC Public Health Ethics Committee and members of the Ethics Subcommittee of the Advisory Committee to the CDC Director (http://www.cdc.gov/od/science/phethics) were consulted.

The workgroup reviewed findings from two unpublished (at the time of discussions, June 12, 2008–June 24, 2009) postlicensure studies on MMRV vaccine and risk for febrile seizures; prelicensure MMRV vaccine data; literature regarding MMR vaccine and varicella vaccine immunogenicity, efficacy, effectiveness, and safety; measles, mumps, rubella, and varicella disease burden; the epidemiology of febrile seizures; the medical and psychosocial importance of febrile seizures; and program implementation considerations. The workgroup also reviewed data on provider and parental attitudes regarding multiple injections and the use of MMRV vaccine in the

context of an increased risk for febrile seizures after the first dose of MMRV vaccine.

Each member of the ACIP workgroup provided their individual interpretation of febrile seizure risk data and input on proposed policy options through two surveys that were subsequently discussed and compiled. In June 2009, ACIP discussed the safety evidence for MMRV vaccine and febrile seizure risk and risk-benefit interpretation and approved policy recommendations for the use of MMRV vaccine compared with MMR vaccine and varicella vaccine. CDC provided guidance regarding implementation of these recommendations.

Scientific Evidence Relevant for Decision-Making

Vaccine Safety

Risk for Febrile Seizure After First Dose of MMRV Vaccine

MMR vaccine is associated with an increased risk for febrile seizures during the first 2 weeks after vaccination (*8*) when the peak in replication of the live attenuated measles virus occurs (6–12 days) (*9*). This risk period has been defined variably in clinical and epidemiologic studies as 8–14 days, 7–12 days, or 5–12 days (*8,10,11*).

In the MMRV vaccine prelicensure studies conducted among children aged 12–23 months, two systemic vaccine-related adverse reactions were reported at a significantly greater rate 0–42 days following vaccination in children who received a first dose of MMRV vaccine (n = 4,497) than in children who received first doses of MMR vaccine and varicella vaccine (n = 2,038) (*6*). Fever (reported as abnormal or elevated ≥102°F [≥39°C] oral equivalent) was observed in 21.5% of MMRV vaccine recipients compared with 14.9% of MMR vaccine and varicella vaccine recipients (risk difference [RD]: 6.6%; 95% confidence interval [CI] = 4.6–8.5). Measles-like rash was observed in 3.0% of MMRV vaccine recipients compared with 2.1% of those receiving MMR vaccine and varicella vaccine (RD: 1.0%; CI = 0.1–1.8) (*6*). Both of these adverse events were reported to occur more frequently 5–12 days postvaccination and typically resolved spontaneously without sequelae.

The reasons for a higher rate of vaccine-associated fever or measles-like rashes after the first dose of MMRV vaccine are not fully understood but might suggest a more vigorous immune response in response to an increase in measles virus replication. The measles, mumps, and rubella viruses in MMRV vaccine are identical and of equal potency to those in the MMR vaccine, but the potency of the varicella-zoster virus is at least seven times higher than the potency in the monovalent varicella vaccine (a minimum of 3.99 $\log_{10}$ plaque forming units [PFUs] compared with 3.13 $\log_{10}$ PFUs) (*6*). However, the measles geometric mean titers (GMTs) measured 6 weeks after vaccination were higher among children who received the first dose of MMRV vaccine than among children who received the first dose of MMR vaccine and varicella vaccine administered at the same visit, whereas the varicella GMTs were similar (*12*). Statistical modeling indicated that the level of the measles antibody titer after receipt of MMRV vaccine was associated positively with the rate of fever and the rate of measles-like rashes (*13*).

Because of the known association between fever and febrile seizures (*14*), Merck and CDC sponsored separate postlicensure studies among larger populations of vaccinated children than were feasible during prelicensure studies to evaluate if a risk for febrile seizures might be associated with the first dose of MMRV vaccine. These studies assessed the febrile seizure risk in different populations using different methods.

Merck sponsored a postlicensure cohort study among children aged 12–60 months (99% of whom were aged 12–23 months) enrolled in a large managed care organization (MCO) (*11*). All potential cases identified by *International Classification of Diseases, Ninth Revision* (ICD-9) codes for seizure from electronic medical records (779.0 [neonatal seizures], 333.2 [myoclonus], 345 [epilepsy], 780.3 [convulsion], 780.31 [simple febrile convulsion], 780.32 [complex febrile convulsion], and 780.39 [other convulsion]) were adjudicated by an independent committee using the Brighton Collaboration definition for seizure (*15*) and documentation of fever (whether measured or not) in the chart. The study groups included 31,298 children who received a first dose of MMRV vaccine during February 2006–June 2007 and 31,298 children who received a first dose of MMR vaccine and varicella vaccine at the same visit during November 2003–January 2006. The two groups were matched individually by age, sex, and calendar date of vaccination. On the basis of findings on fever from prelicensure trials, the primary period of interest to assess the risk for febrile seizures was 5–12 days after vaccination. Another prespecified period of interest was 0–30 days after vaccination because of the biologic plausibility that the replication of the component viruses of the MMRV vaccine might occur during the month after vaccination. The relative risk (RR) for febrile seizures 5–12 days after vaccination was 2.2 (CI = 1.0–4.7; $p<0.05$) among children who received the first dose of MMRV vaccine (rate: 7.0 per 10,000 vaccinations) compared with children who received the first dose of MMR vaccine and varicella vaccine administered at the same visit (rate: 3.2 per 10,000 vaccinations) (Table). These results suggest that, during the 5–12 day postvaccination period, approximately one additional febrile seizure occurred

TABLE. Summary results from Vaccine Safety Datalink (VSD) and Merck-sponsored studies for febrile seizure after the first dose of measles, mumps, rubella and varicella vaccine (MMRV) compared with the first dose of measles, mumps, rubella vaccine (MMR) and varicella vaccine (V) administered at the same visit — United States, 2009

Characteristic	VSD*	Merck-sponsored†
Age/No. subjects, by vaccine	All aged 12–23 months MMRV: n = 83,107 MMR and V: n= 376,354	99% aged 12–23 months MMRV: n = 31,298 MMR and V: n = 31,298
Postvaccination interval		
Week 1–2	7–10 days§ RR: 2.0 (CI = 1.4–2.9) AR: 4.3 per 10,000 (CI = 2.6–5.6)	5–12 days§ RR: 2.2 (CI = 1.0–4.7) AR: 3.8 per 10,000 (CI = 0.3–7.4)
Week 1–6	0–42 days§ RR: 1.5 (CI = 1.1–1.9) AR: 6.2 per 10,000 (CI = 2.0–9.5)	0–30 days RR: 1.1 (CI = 0.7–1.7) AR: 1.3 per 10,000 (CI = -4.5–7.0)

RR = relative risk; AR = attributable risk; CI = 95% confidence interval.
* **Source:** Klein NP, Fireman B, Yih WK, et al. Measles-mumps-rubella-varicella combination vaccine and the risk of febrile seizures. Pediatrics 2010. In press.
† **Source:** Jacobsen SJ, Ackerson BK, Sy LS, et al. Observational safety study of febrile convulsion following first dose MMRV vaccination in a managed care setting. Vaccine 2009;27:4656–61.
§ Statistically significant at <0.05.

among every 2,600 children vaccinated with a first dose of MMRV vaccine compared with children vaccinated with a first dose of MMR vaccine and varicella vaccine administered at the same visit. During 0–30 days postvaccination, the rate of febrile seizure was 14 per 10,000 vaccinations among MMRV vaccine recipients and 13 per 10,000 vaccinations among MMR vaccine and varicella vaccine recipients; the RR was 1.1 (CI = 0.7–1.7; p=0.66).

The CDC-sponsored study was conducted through the Vaccine Safety Datalink (VSD),* a collaboration between CDC and eight MCOs that routinely monitors vaccine safety of new vaccines by near real-time surveillance (*16*). Each MCO site prepares data files containing demographic and medical information on their members and ICD-9 codes assigned to medical encounters. Surveillance conducted through VSD assesses the risk for prespecified health outcomes during prespecified periods after vaccination; the 42-day interval postvaccination is used commonly to study a variety of vaccine adverse events. VSD monitoring of MMRV vaccine detected an increased risk for seizure of any etiology in the interval of 42 days postvaccination among children aged 12–23 months after administration of first dose of MMRV vaccine compared with administration of first dose of MMR vaccine (many children also received varicella vaccine) (*17*). When children who received MMRV vaccine were compared with children who received MMR vaccine and varicella vaccine administered at the same visit, statistically significant clustering of seizures of any etiology was observed 7–10 days after vaccination in both groups, with more seizures observed among children who had received MMRV vaccine (p=0.0001) (*18*).

To further evaluate this finding, VSD initiated a cohort study to determine the risk for febrile seizures 7–10 days and 0–42 days postvaccination among 83,107 children aged 12–23 months who received the first dose of MMRV vaccine during January 2006–October 2008 and a cohort of 376,354 children aged 12–23 months who received the first dose of MMR vaccine and varicella vaccine administered at the same visit during January 2000–October 2008. Investigators reviewed medical records of study children to identify those with a clinical diagnosis of febrile seizure within 42 days after vaccination as defined by ICD-9 codes for seizures (345X [epilepsy] and 780.3X [convulsion]). Poisson regression was used to adjust for age, respiratory season, and other covariates. During 7–10 days after vaccination, the unadjusted rate of febrile seizures was 8.5 per 10,000 vaccinations among MMRV vaccine recipients and 4.2 per 10,000 vaccinations among those who received MMR vaccine and varicella vaccine at the same visit (adjusted RR: 2.0; CI = 1.4–2.9; p = 0.0001) (Table). These results suggest that, during the 7–10 day postvaccination period, approximately one additional febrile seizure occurred among every 2,300 children vaccinated with a first dose of MMRV vaccine compared with children vaccinated with a first dose of MMR vaccine and varicella vaccine administered at the same visit. During 0–42 days postvaccination, the RR was 1.5 (CI = 1.1–1.9; p<0.05). An additional VSD analysis of the febrile seizure risk during 0–30 days postvaccination, (the interval used in the Merck-sponsored study) yielded similar findings as those for the 0–42 days postvaccination interval (*18*).

Risk for Febrile Seizure After Second Dose of MMRV Vaccine

Rates for febrile seizures are lower among children aged 4–6 years (the recommended age for the second dose of MMRV vaccine, MMR vaccine, and varicella vaccine) than among children aged 12–15 months (*14*). In prelicensure studies conducted among children who received their second dose in their second year of life and 3 months after their first dose, the second dose of MMRV vaccine was less likely to cause fever

* Additional information is available at http://www.cdc.gov/od/science/iso/vsd.

than the first dose (*12,13*). Among children aged 4–6 years who received MMRV vaccine for their second dose, the rate of fever was similar to the rate following a second dose of MMR vaccine and varicella vaccine at the same visit (*19*).

Assessing the risk for febrile seizures after the second dose vaccination was not an initial objective of either postlicensure study. In light of findings from first-dose studies, the workgroup requested available data on febrile seizures risk after the second dose from both VSD and Merck. In the data that VSD provided in response to this request, the febrile seizure risk after the second dose was inferred from data among children aged 4–6 years, which is the age when the second dose is routinely recommended. In the data provided by Merck, second-dose subjects were children aged 1–12 years (>95% were aged 4–6 years) who had received MMR vaccine previously, with or without varicella vaccine (for most children in the MMR vaccine and varicella vaccine group, only a second dose of MMR vaccine was administered) (*20*). During 7–10 days following vaccination, the VSD study identified one febrile seizure among 84,653 children aged 4–6 years who received MMRV vaccine and no febrile seizures among 64,663 children the same age who received MMR vaccine and varicella vaccine administered at the same visit (*17*). No febrile seizures occurred during the 5–12 days postvaccination in either group in the Merck-sponsored study (25,212 children received a second dose of MMRV vaccine, and 24,788 received a second dose of MMR vaccine and varicella vaccine at the same visit) (*20*). Therefore, among children aged 4–6 years, postlicensure data do not suggest that children who received MMRV vaccine as a second dose had an increased risk for febrile seizures after vaccination compared with children who received a second dose of MMR vaccine and varicella vaccine at the same visit.

Clinical Importance of Febrile Seizure

Febrile seizures occur most commonly with the fevers caused by typical childhood illnesses (e.g., middle-ear infections, viral upper respiratory tract infections, and roseola) but can be associated with any condition that results in fever, including vaccination. MMR vaccine is associated with an increased risk for febrile seizures occurring 8–14 days after vaccination among children aged <7 years, resulting in an estimated one additional febrile seizure among every 3,000–4,000 children vaccinated with MMR vaccine compared with children not vaccinated during the preceding 30 days (*8*). Studies have not demonstrated an increased risk for febrile seizures during the 30-day period following varicella vaccination, after controlling for the simultaneous administration of MMR vaccine (*21*).

By age 5 years, approximately one in every 25 children will have had a febrile seizure. Febrile seizures usually occur among children aged 6–59 months; the peak age is 14–18 months (*14*), and approximately 97% of febrile seizures occur in children aged <4 years (*22*). Approximately one third of children with a first febrile seizure will have recurrent febrile seizures (*23*). Parents and caregivers of children who have a first febrile seizure are likely to seek medical attention, which commonly includes a visit to an emergency department.

The prognosis for young children who have febrile seizures generally is excellent (*14*). The majority (>90%) of children who have a febrile seizure will not develop epilepsy; certain factors (e.g., presence of complex features during the seizure [duration of seizure >15 minutes, occurrence of more than a single seizure within 24 hours, and focal features], an initial febrile seizure before age 12 months, delayed developmental milestones, or a pre-existing neurologic disorder) and genetic predisposition (i.e., family history of epilepsy) are associated with future development of epilepsy after a febrile seizure (*14,23*). Children who have a febrile seizure soon after MMR vaccination (within 2 weeks or within 7–21 days, depending on the study) are not more likely to have future epilepsy or neurodevelopment disorders than children who have febrile seizures for other reasons (*8,10*). However, one study indicated that these children might have a slightly higher risk for having another febrile seizure than children who had a febrile seizure for other reasons (RR = 1.19; CI = 1.01–1.41) (*10*). Although data on sequelae of febrile seizures after MMRV vaccine are not available, the findings described for MMR vaccine likely also are applicable to MMRV vaccine.

When a child experiences a febrile seizure, negative effects on family members or caregivers can result, including adverse mental and physical health consequences (*24–27*). Parents and caregivers generally consider febrile seizures to be a more severe adverse event than physicians (*28,29*).

Measles, Mumps, Rubella, and Varicella Disease Burden

The burden of disease for measles, mumps, rubella, and varicella in the United States is very low. Endemic transmission for measles and rubella was declared eliminated in 2000 and 2004, respectively (*30,31*). For mumps, the average reported incidence has been 0.1 per 100,000 population since 1993, except in 2006, when a large outbreak occurred primarily affecting the Midwest (*32*), and during 2009–2010, when an outbreak occurred in a religious community in the Northeast (*33*). During 1995–2005, reported varicella incidence declined approximately 90% (*34*). The very low levels of disease are attributed to high population immunity achieved through the use of MMR vaccine and varicella vaccine. After the elimination of measles was achieved, a number of outbreaks of limited size occurred as a result of importation into primarily

unvaccinated populations; these outbreaks did not extend to the highly 2-dose vaccinated populations (*35*).

Immunogenicity and Efficacy of MMRV Vaccine

MMRV vaccine was licensed on the basis of noninferior immunogenicity of the antigenic components compared with simultaneous administration of MMR vaccine and varicella vaccine (*36*). Formal studies to evaluate the clinical efficacy of MMRV vaccine have not been performed; efficacy of MMRV vaccine was inferred from that of MMR vaccine and varicella vaccine on the basis of noninferior immunogenicity.

Programmatic Considerations

Vaccine Coverage

Among children aged 19–35 months, vaccine coverage with ≥1dose of MMR vaccine and varicella vaccine is high; since 1996, coverage with MMR vaccine has been 90%–93%, and in 2008, coverage with varicella vaccine reached 91%. In 2008, coverage with ≥1 dose of MMR vaccine by state ranged from 85.9% to 95.6%; coverage with ≥1 dose of varicella vaccine by state ranged from 77.0% to 95.3% (*37*). For school-aged children, school-entry requirements have proved to be an effective strategy for achieving and maintaining high vaccine coverage (*38*). All states have school-entry requirements for 2 doses of MMR vaccine, and 46 states have school-entry requirements for 1 dose of varicella vaccine. As of September 2009, a total of 22 states had school-entry requirements for 2 doses of varicella vaccine (CDC, unpublished data, 2009). No data were available on the rate of coverage for 2 doses of varicella vaccine.

Maintaining high vaccination coverage is important for disease control. Combination vaccines reduce the number of injections children receive and have the potential to improve vaccination coverage and timeliness of vaccination. However, evidence is limited about the impact of the use of newer combination vaccines on vaccination coverage. Two studies suggested that receipt of *Haemophilus influenzae* type b (Hib)–hepatitis B (HepB) or pediatric diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP)-HepB–inactivated poliovirus vaccine (IPV) combination vaccines was associated with 3%–6% increased coverage for DTaP, IPV, Hib, HepB vaccines compared with the coverage among children who did not receive the combination vaccines (*39,40*). Another study did not find increased coverage for the component vaccines when combination Hib-HepB was used, probably because the coverage rates were already high before introduction of the combination vaccine (*41*). No published literature has specifically assessed the impact of MMRV vaccine on coverage for varicella or other vaccines recommended at age 12–15 months. However, several studies have indicated parent and provider preference for fewer injections at one visit (*42–44*).

Physicians' and Parents' Attitudes on Use of MMRV Vaccine

To better understand attitudes toward use of MMRV vaccine in light of postlicensure findings on febrile seizure risk after the first dose of MMRV vaccine, CDC sponsored a physician survey in 2008 and two parent focus groups in 2009. The physician survey included a nationally representative sample of pediatricians and family physicians (*29,45*). The response rate was 76% for pediatricians (321 of 425) and 71% for family physicians (299 of 424). After being provided with a summary of the findings from the two postlicensure studies of febrile seizure after MMRV vaccination, 59% of pediatricians and 67% of family physicians responded that they would either definitely or probably recommend MMR vaccine and varicella vaccine for the first-dose vaccination for a child aged 12–15 months; 21% and 9%, respectively, would definitely or probably recommend MMRV vaccine; and 20% and 24%, respectively, said they would let the parents decide.[†]

The parent focus groups were conducted in two cities (Kirkland, Washington, and New York City, New York) (*28*). A total of 82 mothers of children aged 7 months–3 years were selected, all of whom reported that they expected their children to receive all or most of the recommended childhood vaccines. Mothers were presented with background materials on febrile seizure risk after the first dose of MMRV vaccine compared with the first dose of MMR vaccine and varicella vaccine. After reviewing and discussing the risks and benefits of both vaccination options, mothers were asked whether they would accept MMRV vaccine for the first-dose vaccination if their pediatrician recommended it; 41% said they would accept vaccination with MMRV vaccine, and 31% said they would refuse. Trust in their pediatrician's judgment was a major factor for mothers' acceptance of MMRV vaccine for their children. Mothers who reported that they would refuse MMRV vaccine said they were unwilling to accept any additional risk over that of MMR vaccine and varicella vaccine, regardless of how small.

[†] Based on response to the following question: "Assuming that your practice has adequate supplies of MMRV, MMR, and varicella vaccines to administer to all your patients, which vaccine(s) would you recommend to a healthy 12–15 month old child?" Answer options were as follows: "1) definitely recommend MMRV, 2) probably recommend MMRV, 3) would let parents choose between MMRV and separate MMR and varicella, 4) probably recommend separate MMR and varicella, and 5) definitely recommend separate MMR and varicella."

Summary and Rationale for MMRV Vaccine Recommendations

Two postlicensure studies (*11,18*) and other related data support the conclusion that use of MMRV vaccine among children aged 12–23 months results in a higher risk for fever and febrile seizures during the 5–12 days after the first dose compared with the use of MMR vaccine and varicella vaccine at the same visit. The approximately twofold increased risk results in an estimated one additional febrile seizure per 2,300–2,600 children vaccinated with the first dose of MMRV vaccine compared with those who receive the first dose with MMR vaccine and varicella vaccine. Although data regarding the risk for febrile seizures after administration of the first dose of MMRV vaccine are available only for children aged 12–23 months, the increased risk for febrile seizures during the 5–12 days postvaccination is likely to be present among children aged ≤47 months because that is the biologic window of vulnerability for febrile seizures in children (approximately 97% of febrile seizures occur in children aged <4 years) (*22*). Compared with no vaccination, MMR vaccine is associated with one additional febrile seizure among every 3,000–4,000 children aged <7 years vaccinated with MMR vaccine (*8*). The risk for febrile seizures during measles illness is higher than the risk after either MMRV vaccine or MMR vaccine (between one in 40 and one in 1,000 children with measles experience a febrile seizure) (*46*).

Results from postlicensure studies do not suggest that children aged 4–6 years who receive the second dose of MMRV vaccine have an increased risk for febrile seizures after vaccination compared with children the same age who receive the second dose of MMR vaccine and varicella vaccine at the same visit (*11,17*). Prelicensure data indicated that the rate of fever after the second dose of MMRV administered to children aged 15–26 months was lower than after the first dose administered to children the same age as either MMRV vaccine or MMR vaccine and varicella vaccine at the same visit (*12*).

The evidence suggests that the two vaccine options (MMRV vaccine or MMR vaccine and varicella vaccine) are equivalent in terms of efficacy, effectiveness, immunogenicity, and burden of disease prevented with the first dose. Evidence to date is not sufficient to demonstrate a clear advantage of either option for the first dose in terms of an impact on program implementation. For the second dose, routine use of MMRV vaccine has the potential to increase second-dose varicella vaccine coverage and thus have a greater impact on controlling varicella disease than MMR vaccine and varicella vaccine, particularly in states that lack school-entry requirements for a second dose of varicella vaccine.

Although a vaccination strategy that would result in the fewest adverse events might be preferred, maximizing choice based on parent or caregiver and physician preference also is an important ethical principle. The decision-making process must include provision of specific information to parents and caregivers about the risk for febrile seizures associated with receipt of the first dose of MMRV vaccine compared with the first dose of MMR vaccine and varicella vaccine.

Use of MMRV vaccine has the benefit of requiring one less injection than the alternative of MMR vaccine and varicella vaccine. The risk for a febrile seizure after the first dose of MMRV vaccine, although low, is higher than after MMR vaccine and varicella vaccine administered as separate injections, and use of MMR vaccine and varicella vaccine avoids this increased risk. Children who have febrile seizures generally have an excellent prognosis. However, first febrile seizures often require a medical visit to an emergency department and are distressing for parents and caregivers. Therefore, parents might prefer to avoid the small increased risk for fever and febrile seizures after the first dose of MMRV vaccine compared with the first dose of MMR vaccine and varicella vaccine administered as separate injections. Given the balance of risks and benefits of a first dose of MMRV vaccine compared with a first dose of MMR vaccine and varicella vaccine, and the importance of individual values and preferences in weighing these risks and benefits, decisions should be made by providers and parents or caregivers on a case-by-case basis.

Recommendations for Use of MMRV Vaccine

ACIP recommendations for use of MMRV vaccine have been summarized (Box). The routinely recommended ages for measles, mumps, rubella, and varicella vaccination continue to be 12–15 months for the first dose and 4–6 years for the second dose.

MMRV vaccine may be administered simultaneously with other vaccines recommended for children aged 12–15 months and 4–6 years. If simultaneous administration is not possible, MMRV vaccine may be administered at any time before or after an inactivated vaccine but at least 28 days before or after another live, attenuated vaccine, except varicella vaccine, for which a minimum interval of 3 months is recommended. Guidance on administration of MMRV vaccine in special situations (e.g., administration of antibody-containing products or tuberculosis screening and skin test reactivity) has been published previously (*47*).

BOX. Summary of recommendations for measles, mumps, rubella and varicella (MMRV) vaccine use

- The routinely recommended ages for measles, mumps, rubella and varicella vaccination continue to be age 12–15 months for the first dose and age 4–6 years for the second dose.
- For the first dose of measles, mumps, rubella, and varicella vaccines at age 12–47 months, either measles, mumps, and rubella (MMR) vaccine and varicella vaccine or MMRV vaccine may be used. Providers who are considering administering MMRV vaccine should discuss the benefits and risks of both vaccination options with the parents or caregivers. Unless the parent or caregiver expresses a preference for MMRV vaccine, CDC recommends that MMR vaccine and varicella vaccine should be administered for the first dose in this age group.
- For the second dose of measles, mumps, rubella, and varicella vaccines at any age (15 months–12 years) and for the first dose at age ≥48 months, use of MMRV vaccine generally is preferred over separate injections of its equivalent component vaccines (i.e., MMR vaccine and varicella vaccine). Considerations should include provider assessment, patient preference, and the potential for adverse events.
- A personal or family (i.e., sibling or parent) history of seizures of any etiology is a precaution for MMRV vaccination. Children with a personal or family history of seizures of any etiology generally should be vaccinated with MMR vaccine and varicella vaccine.

First Dose at Age 12–47 Months

The routinely recommended age for the first dose of measles, mumps, rubella, and varicella vaccines is age 12–15 months; children not vaccinated according to the routine schedule may receive the first dose of MMRV vaccine up to age 12 years. For the first dose of measles, mumps, rubella, and varicella vaccines at age 12–47 months, either MMR vaccine and varicella vaccine or MMRV vaccine may be used. Providers who are considering administering MMRV vaccine should discuss the benefits and risks of both vaccination options with the parents or caregivers. Unless the parent or caregiver expresses a preference for MMRV vaccine, CDC recommends that MMR vaccine and varicella vaccine should be administered for the first dose in this age group.

The discussion with parents or caregivers should focus on helping them understand the risks and benefits using tools including the Vaccine Information Statements. Compared with use of MMR vaccine and varicella vaccine at the same visit, use of MMRV vaccine results in one fewer injection but is associated with a higher risk for fever and febrile seizures 5–12 days after the first dose among children aged 12–23 months (approximately one extra febrile seizure for every 2,300–2,600 MMRV vaccine doses). Use of MMR vaccine and varicella vaccine avoids this increased risk for fever and febrile seizures following MMRV vaccine.

The 47-month cutoff was selected on the basis of the epidemiology of febrile seizures. Approximately 97% of febrile seizures occur in children aged ≤47 months.

Second Dose at Any Age and First Dose at Age ≥48 Months

Although the routinely recommended age for the second dose of measles, mumps, rubella, and varicella vaccines is 4–6 years, the second dose may be administered before age 4 years, provided ≥3 months have elapsed since the first dose. MMRV vaccine is licensed for use among children through age 12 years. For the second dose of measles, mumps, rubella, and varicella vaccines at any age (15 months–12 years) and for the first dose at age ≥48 months, use of MMRV vaccine generally is preferred over separate injections of its equivalent component vaccines (i.e., MMR vaccine and varicella vaccine). Considerations should include provider assessment (i.e., the number of injections, vaccine availability, likelihood of improved coverage, likelihood of patient return, and storage and cost considerations), patient preference, and the potential for adverse events. This recommendation is consistent with ACIP's 2009 provisional general recommendations on combination vaccines (*48*).

Other MMRV Vaccine-Related Guidance

New Precaution for MMRV Vaccine Use

A personal or family (i.e., sibling or parent) history of seizures of any etiology is a precaution[§] for MMRV vaccination. Studies suggest that children who have a personal or family history of febrile seizures or family history of epilepsy are at increased risk for febrile seizures compared with children without such histories (*10,49*). Children with a personal or family history of seizures of any etiology generally should be vaccinated with MMR vaccine and varicella vaccine because the risks for using MMRV vaccine in this group of children generally outweigh the benefits.

Contraindications and Precautions for MMRV Vaccine Use

Contraindications for use of MMRV vaccine include

- history of anaphylactic reaction to neomycin;
- allergic reaction to gelatin, other component of the vaccine, or after previous vaccination with MMRV vaccine, varicella vaccine or MMR vaccine;
- altered immunity (i.e., blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic system);
- primary or acquired immunodeficiency including HIV infections/AIDS, cellular immune deficiencies, hypogammaglobulinemia, and dysgammaglobulinemia;
- family history of congenital or hereditary immunodeficiencies, unless the immune competence of the potential vaccine recipient has been demonstrated;
- systemic immunosuppressive therapy, including oral steroids ≥2 mg/kg of body weight or ≥20 mg/day of prednisone or equivalent for persons who weigh >10 kg, when administered for ≥2 weeks); and
- pregnancy.

Precautions for use of MMRV vaccine include

- recent (≤11 months) receipt of antibody-containing blood product (specific interval depends on dose administered);
- history of thrombocytopenia or thrombocytopenic purpura;
- moderate or severe acute illness with or without fever; and
- a personal or family (i.e., sibling or parent) history of seizures of any etiology.

Use of Antipyretics for Prevention of Febrile Seizures

Studies have not demonstrated that antipyretics (e.g., acetaminophen or ibuprofen) prevent febrile seizures (*50*). Vaccination with either MMR vaccine or MMRV vaccine can cause fever and, rarely, febrile seizures. Most fevers and febrile seizures after administration of a measles-containing vaccine occur 5–12 days after vaccination with the first dose. Parents and caregivers should be counseled about the possibility of fever after receipt of a measles-containing vaccine and educated on timing and measures to control it. Guidance on diagnosis and management of febrile seizures has been published previously (*14,50*).

Reporting of Adverse Events after Vaccination

Clinically significant adverse events that follow vaccination should be reported to the Vaccine Adverse Event Reporting System (VAERS) at http://vaers.hhs.gov/esub/index. Reports can be filed securely online, by mail, or by fax. A VAERS form can be downloaded from the VAERS website or requested by sending an e-mail message to info@vaers.org, by calling telephone 1-800-822-7967, or by sending a faxed request to 1-877-721-0366. Additional information on VAERS or vaccine safety is available at http://vaers.hhs.gov/about/index or by calling telephone 1-800-822-7967.

National Vaccine Injury Compensation Program

The National Vaccine Injury Compensation Program (VICP), established by the National Childhood Vaccine Injury Act of 1986 (as amended), provides a mechanism through which compensation can be paid on behalf of a person determined to have been injured or to have died as a result of receiving a vaccine covered by VICP. The Vaccine Injury Table lists the vaccines covered by VICP and the injuries and conditions (including death) for which compensation might be paid. If the injury or condition is not on the table, or does not occur within the specified time period on the table, persons must prove that the vaccine caused the injury or condition.

Persons of all ages who receive a VICP-covered vaccine might be eligible to file a claim. MMRV vaccine, MMR vaccine and varicella vaccine are covered under VICP.

[§] A precaution is a condition in a recipient that might increase the risk for a serious adverse reaction or that might compromise the ability of the vaccine to produce immunity (e.g., administering measles vaccine to a person with passive immunity to measles from a blood transfusion). A person might experience a more severe reaction to the vaccine than would have otherwise been expected; however, the risk for this happening is less than expected with a contraindication. In general, vaccinations should be deferred when a precaution is present. However, a vaccination might be indicated in the presence of a precaution because the benefit of protection from the vaccine outweighs the risk for an adverse reaction. (CDC. ACIP general recommendations on immunization. MMWR 2006;55[No. RR-15]).

Additional information about VICP is available at http://www.hrsa.gov/vaccinecompensation or by calling telephone 1-800-338-2382.

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Licensure of a Meningococcal Conjugate Vaccine (Menveo) and Guidance for Use --- Advisory Committee on Immunization Practices (ACIP), 2010

Weekly

March 12, 2010 / 59(09);273

On February 19, 2010, the Food and Drug Administration (FDA) licensed a quadrivalent meningococcal conjugate vaccine, MenACWY-CRM (Menveo, Novartis Vaccines and Diagnostics). MenACWY-CRM is licensed as a single dose for use among persons aged 11--55 years. The Advisory Committee on Immunization Practices (ACIP) reviewed data from prelicensure clinical trials on the safety and immunogenicity of MenACWY-CRM. This report summarizes the approved indications for MenACWY-CRM and provides guidance from ACIP for its use. The following guidance for use of MenACWY-CRM is consistent with licensed indications and ACIP recommendations for meningococcal conjugate vaccines.

MenACWY-CRM consists of two components: 1) 10 μg of lyophilized meningococcal serogroup A capsular

polysaccharide conjugated to CRM197 (MenA) and 2) 5 μg each of capsular polysaccharide of serogroup C, Y, and W135 conjugated to CRM197 in 0.5 mL of phosphate buffered saline, which is used to reconstitute the lyophilized MenA component before injection (*1*). The reconstituted vaccine should be used immediately, but may be held at or below 77°F (25°C) for up to 8 hours. MenACWY-CRM is administered as an intramuscular injection, preferably into the deltoid region (*1*).

The capsular polysaccharide serogroups included in MenACWY-CRM are the same as those contained in Sanofi Pasteur's MCV4 (Menactra). In study participants aged 11--18 years, noninferiority of MenACWY-CRM to MCV4 was demonstrated for all four serogroups using the primary endpoint, hSBA seroresponse (serum bactericidal assay using human complement). The proportions of subjects with hSBA seroresponse were statistically higher for serogroups A, W, and Y in the MenACWY-CRM group, compared with the MCV4 group. The clinical relevance of higher postvaccination immune responses is not known (*1*). Safety and reactogenicity profiles were comparable to those observed with MCV4 (*1*).

Guidance for Use of MenACWY-CRM

MenACWY-CRM is licensed by the FDA as a single dose in persons aged 11--55 years (*1*). ACIP recommends quadrivalent meningococcal conjugate vaccine for all persons aged 11--18 years and for persons aged 2--55 years who are at increased risk for meningococcal disease. Persons at increased risk for meningococcal disease include 1) college freshmen living in dormitories, 2) microbiologists who are exposed routinely to isolates of *Neisseria meningitidis*, 3) military recruits, 4) persons who travel to or reside in countries where meningococcal disease is hyperendemic or epidemic, 5) persons who have persistent complement component deficiencies, and 6) persons with anatomic or functional asplenia (*2*). MenACWY-CRM or MCV4 may be used in persons aged 11--55 years, and are preferred to quadrivalent meningococcal polysaccharide vaccine (MPSV4) (*2*). Persons aged 2--10 years who are recommended to receive a meningococcal vaccine should receive MCV4, and persons aged >55 years should receive MPSV4 (*3*).

Severe allergic reaction (e.g., anaphylaxis) after a previous dose of Menveo, any component of this vaccine, or any other CRM197, diphtheria toxoid, or meningococcal-containing vaccine is a contraindication to administration of Menveo. Details regarding the recommended meningococcal vaccination schedule are available at http://www.cdc.gov/vaccines/recs/schedules/default.htm#child. Adverse events after receipt of any vaccine should be reported to the Vaccine Adverse Event Reporting System at http://vaers.hhs.gov.

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Weekly
September 25, 2009 / 58(37);1042-1043

Updated Recommendation from the Advisory Committee on Immunization Practices (ACIP) for Revaccination of Persons at Prolonged Increased Risk for Meningococcal Disease

The Advisory Committee on Immunization Practices (ACIP) recommends quadrivalent meningococcal conjugate vaccine, (MCV4) (Menactra, Sanofi Pasteur, Swiftwater, Pennsylvania) for all persons aged 11--18 years and for persons aged 2--55 years at increased risk for meningococcal disease (*1*--*3*). MCV4 is licensed as a single dose. Because of the high risk for meningococcal disease among certain groups and limited data on duration of protection, at its June 2009 meeting ACIP recommended that persons previously vaccinated with either MCV4 or MPSV4 (Menomune, Sanofi Pasteur) who are at prolonged increased risk for meningococcal disease should be revaccinated with MCV4. Persons who previously were vaccinated at age ≥7 years and are at prolonged increased risk should be revaccinated 5 years after their previous meningococcal vaccine, and persons who previously were vaccinated at ages 2--6 years and are at prolonged increased risk should be revaccinated 3 years after their previous meningococcal vaccine. Persons at prolonged increased risk for meningococcal disease include 1) persons with increased susceptibility such as persistent complement component deficiencies (e.g., C3, properdin, Factor D, and late complement component deficiencies), 2) persons with anatomic or functional asplenia, and 3) persons who have prolonged exposure (e.g., microbiologists routinely working with *Neisseria meningitidis*, or travelers to or residents of countries where meningococcal disease is hyperendemic or epidemic). This report provides the rationale for the new recommendation and updates and replaces previous recommendations for revaccination with MCV4.

ACIP's Meningococcal Vaccine Work Group reviewed data on the risk for meningococcal disease, antibody titer decline, and the safety and immunogenicity of revaccination with MCV4 at 3 years and 5 years after the first dose of MCV4 or MPSV4 (2,3). Persons with prolonged increased risk for meningococcal disease have increased susceptibility to the disease or ongoing increased risk for exposure to N. meningitidis, higher levels of serum bactericidal antibody (SBA) against N. meningitidis can provide these groups increased protection against disease. SBA is a measure of the ability of sera to kill a strain of N. meningitidis in the presence of complement. In clinical trials, a baby rabbit SBA titer of 1:128 was used as a conservative correlate of protection (1). Small subsets of subjects from the MCV4 prelicensure clinical trial were revaccinated 3 years (n = 76) and 5 years (n = 134) after receiving MCV4. Of 71 persons aged 11--18 years at primary vaccination who had been vaccinated with MCV4 3 years previously, 75% and 86% had SBA titers greater than 1:128 for serogroups C and Y, respectively, before revaccination. Of 108 persons aged 2--10 years at primary vaccination who had been vaccinated with MCV4 5 years previously, 55% and 94% had SBA titers greater than 1:128 for serogroups C and Y, respectively, before revaccination. All persons revaccinated with MCV4 in these studies achieved SBA titers greater than 1:128 for serogroups C and Y. Approximately 50%--70% of persons in both the previously vaccinated (n = 210) and vaccine naive groups (n = 323) reported mild to moderate local and systemic adverse events after revaccination (or initial vaccination) with MCV4. However, no serious adverse events were reported in either group (Sanofi Pasteur, unpublished data, 2009).

On the basis of these data, expert opinion of the workgroup members, and feedback from partner organizations, the workgroup proposed that persons at prolonged increased risk for meningococcal disease be revaccinated with MCV4. ACIP approved this proposal at its June 24, 2009, meeting. Persons who previously were vaccinated at age ≥7 years and are at prolonged increased risk should be revaccinated 5 years after their previous meningococcal vaccine. Persons who previously were vaccinated at ages 2--6 years and are at prolonged increased risk should be revaccinated 3 years after their previous meningococcal vaccine. Persons who remain in one of these increased risk groups indefinitely should continue to be revaccinated at 5-year intervals.

Although the duration of protection from MCV4 is unknown, most entering college students will have received MCV4 within the preceding 4 years. Because of the limited period of increased risk, ACIP currently does not recommend that college freshmen living in dormitories who were previously vaccinated with MCV4 be revaccinated. However, college freshmen living in dormitories who were vaccinated with MPSV4 ≥5 years previously are recommended to be vaccinated with MCV4. Information regarding MCV4 and other recommendations for persons aged 2--55 years (*2*,*3*), including a routine recommendation for vaccination with MCV4 in persons aged 11--18 years (*4*), has been published previously.

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Licensure of a 13-Valent Pneumococcal Conjugate Vaccine (PCV13) and Recommendations for Use Among Children --- Advisory Committee on Immunization Practices (ACIP), 2010

Weekly

March 12, 2010 / 59(09);258-261

On February 24, 2010, a 13-valent pneumococcal conjugate vaccine (PCV13 [Prevnar 13, Wyeth Pharmaceuticals Inc., a subsidiary of Pfizer Inc.]) was licensed by the Food and Drug Administration (FDA) for prevention of invasive pneumococcal disease (IPD) caused by the 13 pneumococcal serotypes covered by the vaccine and for prevention of otitis media caused by serotypes in the 7-valent pneumococcal conjugate vaccine formulation (PCV7 [Prevnar, Wyeth]). PCV13 is approved for use among children aged 6 weeks--71 months and succeeds PCV7, which was licensed by FDA in 2000. The Pneumococcal Vaccines Work Group of the Advisory Committee on Immunization Practices (ACIP) reviewed available data on the

immunogenicity, safety, and cost-effectiveness of PCV13, and on estimates of the vaccine-preventable pneumococcal disease burden. The working group then presented policy options for consideration of the full ACIP. This report summarizes recommendations approved by ACIP on February 24, 2010, for 1) routine vaccination of all children aged 2--59 months with PCV13, 2) vaccination with PCV13 of children aged 60--71 months with underlying medical conditions that increase their risk for pneumococcal disease or complications, and 3) PCV13 vaccination of children who previously received 1 or more doses of PCV7 (*1*). CDC guidance for vaccination providers regarding transition from PCV7 to the PCV13 immunization program also is included.

Prevnar 13 Licensure

Vaccine formulation. PCV13 contains polysaccharides of the capsular antigens of *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F, individually conjugated to a nontoxic diphtheria CRM197 (CRM, cross-reactive material) carrier protein. A 0.5-mL PCV13 dose contains approximately 2 μg of polysaccharide from each of 12 serotypes and approximately 4 μg of polysaccharide from serotype 6B; the total concentration of CRM197 is approximately 34 μg. The vaccine contains 0.125 mg of aluminum as aluminum phosphate adjuvant and no thimerosal preservative. PCV13 is administered intramuscularly and is available in single-dose, prefilled syringes that do not contain latex (*2*).

Immunogenicity profile. The immunogenicity of PCV13 was evaluated in a randomized, double-blind, active-controlled trial in which 663 U.S. infants received at least 1 dose of PCV13 or PCV7 (*3*). To compare PCV13 antibody responses with those for PCV7, criteria for noninferior immunogenicity after 3 and 4 doses of PCV13 (pneumococcal immunoglobulin G [IgG] antibody concentrations measured by enzyme immunoassay) were defined for the seven serotypes common to PCV7 and PCV13 (4, 6B, 9V, 14, 18C, 19F, and 23F) and for the six additional serotypes in PCV13 (serotypes 1, 3, 5, 6A, 7F, and 19A). Functional antibody responses were measured by opsonophagocytosis assay (OPA) in a subset of the study population. Evaluation of these immunologic parameters indicated that PCV13 induced levels of antibodies that were comparable to those induced by PCV7 and shown to be protective against IPD (*3*).

Among infants receiving the 3-dose primary series, responses to three PCV13 serotypes (the shared serotypes 6B and 9V, and new serotype 3) did not meet the prespecified, primary endpoint criterion (percentage of subjects achieving an IgG seroresponse of ≥0.35 μg/mL 1 month after the third dose); however, detectable OPA antibodies to each of these three serotypes indicated the presence of functional antibodies (*3*). The percentages of subjects with an OPA titer ≥1:8 were similar for the seven common serotypes among PCV13 recipients (range: 90%--100%) and PCV7 recipients (range: 93%--100%); the proportion of PCV13 recipients with an OPA titer ≥1:8 was >90% for all of the 13 serotypes (*3*).

After the fourth dose, the IgG geometric mean concentrations (GMCs) were comparable for 12 of the 13 serotypes; the noninferiority criterion was not met for serotype 3. However, measurable OPA titers were present for all serotypes after the fourth dose; the percentage of PCV13 recipients with an OPA titer ≥1:8 ranged from 97% to 100% for the 13 serotypes and was 98% for serotype 3 (*3*).

A schedule of 3 doses of PCV7 followed by 1 dose of PCV13 resulted in somewhat lower IgG GMCs for the six additional serotypes compared with a 4-dose PCV13 series. However, the OPA responses after the fourth dose were comparable for the two groups, and the clinical relevance of these lower antibody responses is not known. The single dose of PCV13 among children aged ≥12 months who had received 3 doses of PCV7 elicited IgG immune responses to the six additional serotypes that were comparable to those after a 3-dose infant PCV13 series (*3*).

Safety profile. The safety of PCV13 was assessed in 13 clinical trials in which 4,729 healthy infants and toddlers were administered at least 1 dose of PCV13 and 2,760 children received at least 1 dose of PCV7, concomitantly with other routine pediatric vaccines. The most commonly reported (more than 20% of subjects) solicited adverse reactions that occurred within 7 days after each dose of PCV13 were injection-site reactions, fever, decreased appetite, irritability, and increased or decreased sleep (*2*). The incidence and severity of solicited local reactions at the injection site (pain/tenderness, erythema, and induration/swelling) and solicited systemic reactions (irritability, drowsiness/increased sleep, decreased appetite, fever, and restless sleep/decreased sleep) were similar in the PCV13 and PCV7 groups. These data

suggest that the safety profiles of PCV13 and PCV7 are comparable (*2*); CDC will conduct postlicensure monitoring for adverse events, and the manufacturer will conduct a Phase IV study.

Supportive data for safety outcomes were provided by a catch-up study among 354 children aged 7--71 months who received at least 1 dose of PCV13. In addition, an open label study was conducted among 284 healthy U.S. children aged 15--59 months who had previously received 3 or 4 doses of PCV7 (*2*). Among these children, the frequency and severity of solicited local reactions and systemic adverse reactions after 1 dose of PCV13 were comparable to those among children receiving their fourth dose of PCV13 (*2*).

Indications and Guidance for Use

ACIP recommends PCV13 for all children aged 2--59 months. ACIP also recommends PCV13 for children aged 60--71 months with underlying medical conditions that increase their risk for pneumococcal disease or complications (Table 1).

No previous PCV7/PCV13 vaccination. The ACIP recommendation for routine vaccination with PCV13 and the immunization schedules for infants and toddlers through age 59 months who have not received any previous PCV7 or PCV13 doses are the same as those previously published for PCV7 (*4*,*5*). PCV13 is recommended as a 4-dose series at ages 2, 4, 6, and 12--15 months. Infants receiving their first dose at age ≤6 months should receive 3 doses of PCV13 at intervals of approximately 8 weeks (the minimum interval is 4 weeks). The fourth dose is recommended at age 12--15 months, and at least 8 weeks after the third dose (Table 2).

Children aged 7--59 months who have not been vaccinated with PCV7 or PCV13 previously should receive 1 to 3 doses of PCV13, depending on their age at the time when vaccination begins and whether underlying medical conditions are present (Table 2). Children aged 24--71 months with chronic medical conditions that increase their risk for pneumococcal disease should receive 2 doses of PCV13. Interruption of the vaccination schedule does not require reinstitution of the entire series or the addition of extra doses.

Incomplete PCV7/ PCV13 vaccination. Infants and children who have received 1 or more doses of PCV7 should complete the immunization series with PCV13 (Table 3). Children aged 12--23 months who have received 3 doses of PCV7 before age 12 months are recommended to receive 1 dose of PCV13, given at least 8 weeks after the last dose of PCV7. No additional PCV13 doses are recommended for children aged 12--23 months who received 2 or 3 doses of PCV7 before age 12 months and at least 1 dose of PCV13 at age ≥12 months.

Similar to the previous ACIP recommendation for use of PCV7 (*6*), 1 dose of PCV13 is recommended for all healthy children aged 24--59 months with any incomplete PCV schedule (PCV7 or PCV13). For children aged 24--71 months with underlying medical conditions who have received any incomplete schedule of <3 doses of PCV (PCV7 or PCV13) before age 24 months, 2 doses of PCV13 are recommended. For children with underlying medical conditions who have received 3 doses of PCV (PCV7 or PCV13) a single dose of PCV13 is recommended through age 71 months. The minimum interval between doses is 8 weeks.

Complete PCV7 vaccination. A single supplemental dose of PCV13 is recommended for all children aged 14--59 months who have received 4 doses of PCV7 or another age-appropriate, complete PCV7 schedule (Table 3). For children who have underlying medical conditions, a single supplemental PCV13 dose is recommended through age 71 months. This includes children who have previously received the 23-valent pneumococcal polysaccharide vaccine (PPSV23). PCV13 should be given at least 8 weeks after the last dose of PCV7 or PPSV23.

In addition, a single dose of PCV13 may be administered to children aged 6--18 years who are at increased risk for IPD because of sickle cell disease, human immunodeficiency virus (HIV) infection or other immunocompromising condition, cochlear implant, or cerebrospinal fluid leaks, regardless of whether they have previously received PCV7 or PPSV23. Routine use of PCV13 is not recommended for healthy children aged ≥5 years.

Precautions and Contraindications

Before administering PCV13, vaccination providers should consult the package insert for precautions, warnings, and contraindications. Vaccination with PCV13 is contraindicated among persons known to have severe allergic reaction (e.g., anaphylaxis) to any component of PCV13 or PCV7 or to any diphtheria toxoid-containing vaccine (*2*).

Transition from PCV7 to PCV13

When PCV13 is available in the vaccination provider's office, unvaccinated children and children incompletely vaccinated with PCV7 should complete the immunization series with PCV13. If the only pneumococcal conjugate vaccine available in a provider's office is PCV7, that vaccine should be provided to children and infants who are due for vaccination; these children should complete their series with PCV13 at subsequent visits. Children for whom the supplemental PCV13 dose is recommended should receive it at their next medical visit, at least 8 weeks after the last dose of PCV7.

According to the manufacturer, supplies of PCV13 should be adequate to allow providers to vaccinate children according to the routine immunization schedule and provide a supplemental dose as recommended. For private vaccine supplies, providers should contact Pfizer's customer service department (telephone, 800-666-7248) with questions about purchasing quantities of PCV13 or returning PCV7 for credit. For public vaccine supplies, including Vaccines for Children Program vaccine, providers should contact their state/local immunization program to determine when PCV13 will become available for ordering in their jurisdiction and what to do with unused supplies of PCV7.

The PCV13 Vaccine Information Statement is available at http://www.cdc.gov/vaccines/pubs/vis/default.htm. Details about the routine pneumococcal conjugate vaccination schedule are available at http://www.cdc.gov/vaccines/recs/schedules/default.htm#child. Adverse events after receipt of any vaccine should be reported to the Vaccine Adverse Event Reporting System at http://vaers.hhs.gov.

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1. CDC. ACIP provisional recommendations for use of 13-valent pneumococcal conjugate vaccine (PCV13) among infants and children. Available at http://www.cdc.gov/vaccines/recs/provisional/downloads/pcv13-mar-2010-508.pdf. Accessed March 9, 2010.
2. Food and Drug Administration. Vaccines: approved products. Prevnar 13 (pneumococcal 13-valent conjugate vaccine). Available at http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm201667.htm. Accessed March 5, 2010
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4. CDC. Preventing pneumococcal disease among infants and young children: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2000;49(No. RR-9).
5. CDC. Recommended immunization schedule for persons aged 0 through 18 years---United States, 2010. MMWR 2010;58(51&52).
6. CDC. Updated recommendation from the Advisory Committee on Immunization Practices (ACIP) for use of 7-valent pneumococcal conjugate vaccine (PCV7) in children aged 24--59 months who are not completely vaccinated. MMWR 2008;57:343--4.

TABLE 1. Underlying medical conditions that are indications for pneumococcal vaccination among children, by risk group --- Advisory Committee on Immunization Practices (ACIP), United States, 2010

Risk group	Condition

Immunocompetent children	Chronic heart disease*
	Chronic lung disease†
	Diabetes mellitus
	Cerebrospinal fluid leaks
	Cochlear implant
Children with functional or anatomic asplenia	Sickle cell disease and other hemoglobinopathies
	Congenital or acquired asplenia, or splenic dysfunction
Children with immunocompromising conditions	HIV infection
	Chronic renal failure and nephrotic syndrome
	Diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, and Hodgkin disease; or solid organ transplantation
	Congenital immunodeficiency§

* Particularly cyanotic congenital heart disease and cardiac failure.

† Including asthma if treated with prolonged high-dose oral corticosteroids.

§ Includes B- (humoral) or T-lymphocyte deficiency; complement deficiencies, particularly C1, C2, C3, and C4 deficiency; and phagocytic disorders (excluding chronic granulomatous disease).

TABLE 2. Recommended routine vaccination schedule for 13-valent pneumococcal conjugate vaccine (PCV13) among infants and children who have not received previous doses of 7-valent vaccine (PCV7) or PCV13, by age at first dose --- Advisory Committee on Immunization Practices (ACIP), United States, 2010

Age at first dose (mos)	Primary PCV13 series*	PCV13 booster dose†
		1 dose at age 12--

2--6	3 doses	15 mos
7--11	2 doses	1 dose at age 12--15 mos
12--23	2 doses	---
24--59 (Healthy children)	1 dose	---
24--71 (Children with certain chronic diseases or immunocompromising conditions§)	2 doses	---

* Minimum interval between doses is 8 weeks except for children vaccinated at age <12 months for whom minimum interval between doses is 4 weeks. Minimum age for administration of first dose is 6 weeks.

† Given at least 8 weeks after the previous dose.

§ For complete list of conditions, see Table 1.

TABLE 3. Recommended transition schedule from 7-valent pneumococcal conjugate vaccine (PCV7) to 13-valent vaccine (PCV13) vaccination among infants and children, according to number of previous PCV7 doses received --- Advisory Committee on Immunization Practices (ACIP), United States, 2010

Infant series			**Booster dose**	**Supplemental PCV13 dose**
2 mos	**4 mos**	**6 mos**	**≥12 mos***	**14--59 mos†**
PCV7	PCV13	PCV13	PCV13	---
PCV7	PCV7	PCV13	PCV13	---
PCV7	PCV7	PCV7	PCV13	---
PCV7	PCV7	PCV7	PCV7	PCV13

* No additional PCV13 doses are indicated for children age 12--23 months who have received 2 or 3 doses of PCV before age 12 months and at least 1 dose of PCV13 at age ≥12 months.

† For children with underlying medical conditions (see Table 1), a single supplemental PCV13 dose is recommended through age 71 months

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Weekly

August 7, 2009 / 58(30);829-830

Updated Recommendations of the Advisory Committee on Immunization Practices (ACIP) Regarding Routine Poliovirus Vaccination

This report updates Advisory Committee on Immunization Practices (ACIP) recommendations for routine poliovirus vaccination. These updates aim to 1) emphasize the importance of the booster dose at age ≥4 years, 2) extend the minimum interval from dose 3 to dose 4 from 4 weeks to 6 months, 3) add a precaution for the use of minimum intervals in the first 6 months of life, and 4) clarify the poliovirus vaccination schedule when specific combination vaccines are used.

On June 17, 1999, ACIP recommended that all poliovirus vaccine administered in the United States be an inactivated poliovirus vaccine (IPV) beginning January 1, 2000. This policy was implemented to eliminate the risk for vaccine-associated paralytic poliomyelitis, a rare condition that has been associated with use of the live oral poliovirus vaccine (OPV). Since 1999, no OPV has been distributed in the United States. Under these ACIP recommendations, the routine IPV vaccination schedule in the United States consists of 4 doses administered at ages 2 months, 4 months, 6--18 months, and 4--6 years with the minimum interval between all IPV doses as 4 weeks (*1*,*2*).

Since the ACIP recommendation was made 10 years ago, three different combination vaccines containing IPV have been licensed for routine use in the United States (Table). Because of potential confusion in using different vaccine products for routine and catch-up immunization, ACIP recommends the following:

- The 4-dose IPV series should continue to be administered at ages 2 months, 4 months, 6--18 months, and 4--6 years.
- The final dose in the IPV series should be administered at age ≥4 years regardless of the number of previous doses.
- The minimum interval from dose 3 to dose 4 is extended from 4 weeks to 6 months.
- The minimum interval from dose 1 to dose 2, and from dose 2 to dose 3, remains 4 weeks.
- The minimum age for dose 1 remains age 6 weeks.

ACIP also is making a new recommendation concerning the use of minimum age and minimum intervals for children in the first 6 months of life. Use of the minimum age and minimum intervals for vaccine administration in the first 6 months of life are recommended only if the vaccine recipient is at risk for imminent exposure to circulating poliovirus (e.g., during an outbreak or because of travel to a polio-endemic region). ACIP is making this precaution because shorter intervals and earlier start dates lead to lower seroconversion rates (*3*--*5*).

In addition, ACIP is clarifying the poliovirus vaccination schedule to be used for specific combination vaccines. When DTaP-IPV/Hib* (Pentacel) is used to provide 4 doses at ages 2, 4, 6, and 15--18 months,

an additional booster dose of age-appropriate IPV-containing vaccine (IPV [Ipol] or DTaP-IPV† [Kinrix]) should be administered at age 4--6 years. This will result in a 5-dose IPV vaccine series, which is considered acceptable by ACIP. DTaP-IPV/Hib is not indicated for the booster dose at age 4--6 years. ACIP recommends that the minimum interval from dose 4 to dose 5 should be at least 6 months to provide an optimum booster response. In accordance with existing recommendations, if a child misses an IPV dose at age 4--6 years, the child should receive a booster dose as soon as feasible (*2*).

References

1. CDC. Recommendations of the Advisory Committee on Immunization Practices: revised recommendations for routine poliomyelitis vaccination. MMWR 1999;48:590.
2. CDC. Poliomyelitis prevention in the United States: updated recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2000;49(No. RR-5).
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* Diphtheria and tetanus toxoids and acellular pertussis adsorbed, inactivated poliovirus, and *Haemophilus* b conjugate (tetanus toxoid conjugate) vaccine.

† Diphtheria and tetanus toxoids and acellular pertussis adsorbed, and inactivated poliovirus vaccine.

TABLE. Currently licensed vaccines containing inactivated poliovirus vaccine (IPV) --- United States, 2009*

Vaccine composition	Trade name	Manufacturer	Approved use in ACIP† routine schedule	Comments
IPV	Ipol (Poliovax§)	Sanofi Pasteur	2, 4, 6--18 mos, and 4--6 yrs	Approved for use in infants, children, and adults¶
DTaP-HepB-IPV**	Pediarix	GlaxoSmithKline	2, 4, and 6 mos	Approved for first 3 doses of IPV through age 6 yrs††
DTaP-IPV/Hib§§	Pentacel	Sanofi Pasteur	2, 4, 6, and 15--18 mos	Approved for 4 doses of IPV through age 4 yrs¶¶
DTaP-IPV***	Kinrix	GlaxoSmithKline	4--6 yrs	Approved for booster dose at age 4--6 yrs†††

* As of August 5, 2009.

† Advisory Committee on Immunization Practices. Full schedule available at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5751a5.htm.

§ Not currently distributed in the United States.

¶ Package insert available at http://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm133479.pdf.

** Diphtheria and tetanus toxoids and acellular pertussis adsorbed, hepatitis B (recombinant), and inactivated poliovirus vaccine combined.

†† Package insert available at http://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm168055.pdf.

§§ Diphtheria and tetanus toxoids and acellular pertussis adsorbed, inactivated poliovirus, and *Haemophilus* b conjugate (tetanus toxoid conjugate) vaccine.

¶¶ Package insert available at http://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm109810.pdf.

*** Diphtheria and tetanus toxoids and acellular pertussis adsorbed, and inactivated poliovirus vaccine.

††† Package insert available at http://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm107220.pdf.

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Date last reviewed: 8/6/2009

Recommended Immunization Schedule for Persons Aged 0 Through 6 Years—United States • 2010

For those who fall behind or start late, see the catch-up schedule

Vaccine ▼ Age ▶	Birth	1 month	2 months	4 months	6 months	12 months	15 months	18 months	19–23 months	2–3 years	4–6 years
Hepatitis B[1]	HepB	HepB			HepB						
Rotavirus[2]			RV	RV	RV[2]						
Diphtheria, Tetanus, Pertussis[3]			DTaP	DTaP	DTaP	*see footnote[3]*	DTaP				DTaP
Haemophilus influenzae type b[4]			Hib	Hib	Hib[4]	Hib					
Pneumococcal[5]			PCV	PCV	PCV	PCV				PPSV	
Inactivated Poliovirus[6]			IPV	IPV	IPV						IPV
Influenza[7]					Influenza (Yearly)						
Measles, Mumps, Rubella[8]						MMR		*see footnote[8]*			MMR
Varicella[9]						Varicella		*see footnote[9]*			Varicella
Hepatitis A[10]						HepA (2 doses)				HepA Series	
Meningococcal[11]										MCV	

Range of recommended ages for all children except certain high-risk groups

Range of recommended ages for certain high-risk groups

This schedule includes recommendations in effect as of December 15, 2009. Any dose not administered at the recommended age should be administered at a subsequent visit, when indicated and feasible. The use of a combination vaccine generally is preferred over separate injections of its equivalent component vaccines. Considerations should include provider assessment, patient preference, and the potential for adverse events. Providers should consult the relevant Advisory Committee on Immunization Practices statement for detailed recommendations: **http://www.cdc.gov/vaccines/pubs/acip-list.htm**. Clinically significant adverse events that follow immunization should be reported to the Vaccine Adverse Event Reporting System (VAERS) at **http://www.vaers.hhs.gov** or by telephone, **800-822-7967.**

1. **Hepatitis B vaccine (HepB).** (Minimum age: birth)
   At birth:
   - Administer monovalent HepB to all newborns before hospital discharge.
   - If mother is hepatitis B surface antigen (HBsAg)-positive, administer HepB and 0.5 mL of hepatitis B immune globulin (HBIG) within 12 hours of birth.
   - If mother's HBsAg status is unknown, administer HepB within 12 hours of birth. Determine mother's HBsAg status as soon as possible and, if HBsAg-positive, administer HBIG (no later than age 1 week).

   After the birth dose:
   - The HepB series should be completed with either monovalent HepB or a combination vaccine containing HepB. The second dose should be administered at age 1 or 2 months. Monovalent HepB vaccine should be used for doses administered before age 6 weeks. The final dose should be administered no earlier than age 24 weeks.
   - Infants born to HBsAg-positive mothers should be tested for HBsAg and antibody to HBsAg 1 to 2 months after completion of at least 3 doses of the HepB series, at age 9 through 18 months (generally at the next well-child visit).
   - Administration of 4 doses of HepB to infants is permissible when a combination vaccine containing HepB is administered after the birth dose. The fourth dose should be administered no earlier than age 24 weeks.
2. **Rotavirus vaccine (RV).** (Minimum age: 6 weeks)
   - Administer the first dose at age 6 through 14 weeks (maximum age: 14 weeks 6 days). Vaccination should not be initiated for infants aged 15 weeks 0 days or older.
   - The maximum age for the final dose in the series is 8 months 0 days
   - If Rotarix is administered at ages 2 and 4 months, a dose at 6 months is not indicated.
3. **Diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP).** (Minimum age: 6 weeks)
   - The fourth dose may be administered as early as age 12 months, provided at least 6 months have elapsed since the third dose.
   - Administer the final dose in the series at age 4 through 6 years.
4. ***Haemophilus influenzae* type b conjugate vaccine (Hib).** (Minimum age: 6 weeks)
   - If PRP-OMP (PedvaxHIB or Comvax [HepB-Hib]) is administered at ages 2 and 4 months, a dose at age 6 months is not indicated.
   - TriHiBit (DTaP/Hib) and Hiberix (PRP-T) should not be used for doses at ages 2, 4, or 6 months for the primary series but can be used as the final dose in children aged 12 months through 4 years.
5. **Pneumococcal vaccine.** (Minimum age: 6 weeks for pneumococcal conjugate vaccine [PCV]; 2 years for pneumococcal polysaccharide vaccine [PPSV])
   - PCV is recommended for all children aged younger than 5 years. Administer 1 dose of PCV to all healthy children aged 24 through 59 months who are not completely vaccinated for their age.
   - Administer PPSV 2 or more months after last dose of PCV to children aged 2 years or older with certain underlying medical conditions, including a cochlear implant. See *MMWR* 1997;46(No. RR-8).
6. **Inactivated poliovirus vaccine (IPV)** (Minimum age: 6 weeks)
   - The final dose in the series should be administered on or after the fourth birthday and at least 6 months following the previous dose.
   - If 4 doses are administered prior to age 4 years a fifth dose should be administered at age 4 through 6 years. See *MMWR* 2009;58(30):829–30.
7. **Influenza vaccine (seasonal).** (Minimum age: 6 months for trivalent inactivated influenza vaccine [TIV]; 2 years for live, attenuated influenza vaccine [LAIV])
   - Administer annually to children aged 6 months through 18 years.
   - For healthy children aged 2 through 6 years (i.e., those who do not have underlying medical conditions that predispose them to influenza complications), either LAIV or TIV may be used, except LAIV should not be given to children aged 2 through 4 years who have had wheezing in the past 12 months.
   - Children receiving TIV should receive 0.25 mL if aged 6 through 35 months or 0.5 mL if aged 3 years or older.
   - Administer 2 doses (separated by at least 4 weeks) to children aged younger than 9 years who are receiving influenza vaccine for the first time or who were vaccinated for the first time during the previous influenza season but only received 1 dose.
   - For recommendations for use of influenza A (H1N1) 2009 monovalent vaccine see *MMWR* 2009;58(No. RR-10).
8. **Measles, mumps, and rubella vaccine (MMR).** (Minimum age: 12 months)
   - Administer the second dose routinely at age 4 through 6 years. However, the second dose may be administered before age 4, provided at least 28 days have elapsed since the first dose.
9. **Varicella vaccine.** (Minimum age: 12 months)
   - Administer the second dose routinely at age 4 through 6 years. However, the second dose may be administered before age 4, provided at least 3 months have elapsed since the first dose.
   - For children aged 12 months through 12 years the minimum interval between doses is 3 months. However, if the second dose was administered at least 28 days after the first dose, it can be accepted as valid.
10. **Hepatitis A vaccine (HepA).** (Minimum age: 12 months)
    - Administer to all children aged 1 year (i.e., aged 12 through 23 months). Administer 2 doses at least 6 months apart.
    - Children not fully vaccinated by age 2 years can be vaccinated at subsequent visits
    - HepA also is recommended for older children who live in areas where vaccination programs target older children, who are at increased risk for infection, or for whom immunity against hepatitis A is desired.
11. **Meningococcal vaccine.** (Minimum age: 2 years for meningococcal conjugate vaccine [MCV4] and for meningococcal polysaccharide vaccine [MPSV4])
    - Administer MCV4 to children aged 2 through 10 years with persistent complement component deficiency, anatomic or functional asplenia, and certain other conditions placing tham at high risk.
    - Administer MCV4 to children previously vaccinated with MCV4 or MPSV4 after 3 years if first dose administered at age 2 through 6 years. See *MMWR* 2009;58:1042–3.

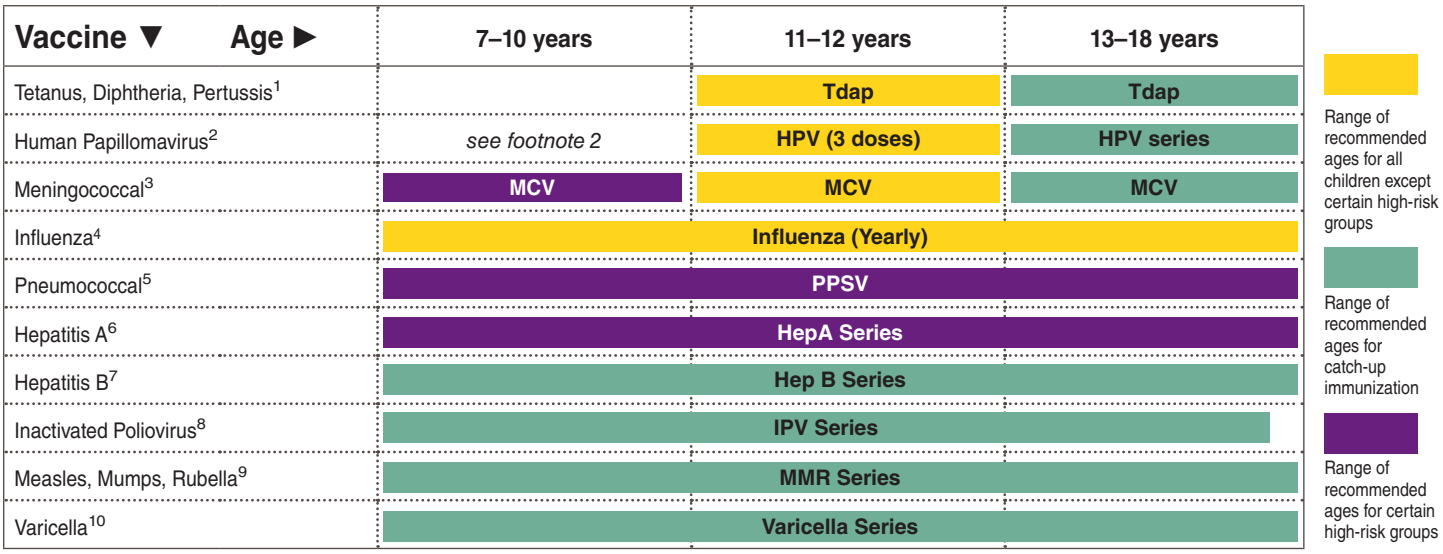
The Recommended Immunization Schedules for Persons Aged 0 through 18 Years are approved by the Advisory Committee on Immunization Practices (**http://www.cdc.gov/vaccines/recs/acip**), the American Academy of Pediatrics (**http://www.aap.org**), and the American Academy of Family Physicians (**http://www.aafp.org**).

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Recommended Immunization Schedule for Persons Aged 7 Through 18 Years—United States • 2010

For those who fall behind or start late, see the schedule below and the catch-up schedule



This schedule includes recommendations in effect as of December 15, 2009. Any dose not administered at the recommended age should be administered at a subsequent visit, when indicated and feasible. The use of a combination vaccine generally is preferred over separate injections of its equivalent component vaccines. Considerations should include provider assessment, patient preference, and the potential for adverse events. Providers should consult the relevant Advisory Committee on Immunization Practices statement for detailed recommendations: **http://www.cdc.gov/vaccines/pubs/acip-list.htm**. Clinically significant adverse events that follow immunization should be reported to the Vaccine Adverse Event Reporting System (VAERS) at **http://www.vaers.hhs.gov** or by telephone, **800-822-7967.**

1. **Tetanus and diphtheria toxoids and acellular pertussis vaccine (Tdap).** (Minimum age: 10 years for Boostrix and 11 years for Adacel)
   - Administer at age 11 or 12 years for those who have completed the recommended childhood DTP/DTaP vaccination series and have not received a tetanus and diphtheria toxoid (Td) booster dose.
   - Persons aged 13 through 18 years who have not received Tdap should receive a dose.
   - A 5-year interval from the last Td dose is encouraged when Tdap is used as a booster dose; however, a shorter interval may be used if pertussis immunity is needed.
2. **Human papillomavirus vaccine (HPV).** (Minimum age: 9 years)
   - Two HPV vaccines are licensed: a quadrivalent vaccine (HPV4) for the prevention of cervical, vaginal and vulvar cancers (in females) and genital warts (in females and males), and a bivalent vaccine (HPV2) for the prevention of cervical cancers in females.
   - HPV vaccines are most effective for both males and females when given before exposure to HPV through sexual contact.
   - HPV4 or HPV2 is recommended for the prevention of cervical precancers and cancers in females.
   - HPV4 is recommended for the prevention of cervical, vaginal and vulvar precancers and cancers and genital warts in females.
   - Administer the first dose to females at age 11 or 12 years.
   - Administer the second dose 1 to 2 months after the first dose and the third dose 6 months after the first dose (at least 24 weeks after the first dose).
   - Administer the series to females at age 13 through 18 years if not previously vaccinated.
   - HPV4 may be administered in a 3-dose series to males aged 9 through 18 years to reduce their likelihood of acquiring genital warts.
3. **Meningococcal conjugate vaccine (MCV4).**
   - Administer at age 11 or 12 years, or at age 13 through 18 years if not previously vaccinated.
   - Administer to previously unvaccinated college freshmen living in a dormitory.
   - Administer MCV4 to children aged 2 through 10 years with persistent complement component deficiency, anatomic or functional asplenia, or certain other conditions placing them at high risk.
   - Administer to children previously vaccinated with MCV4 or MPSV4 who remain at increased risk after 3 years (if first dose administered at age 2 through 6 years) or after 5 years (if first dose administered at age 7 years or older). Persons whose only risk factor is living in on-campus housing are not recommended to receive an additional dose. See *MMWR* 2009;58:1042–3.
4. **Influenza vaccine (seasonal).**
   - Administer annually to children aged 6 months through 18 years.
   - For healthy nonpregnant persons aged 7 through 18 years (i.e., those who do not have underlying medical conditions that predispose them to influenza complications), either LAIV or TIV may be used.
   - Administer 2 doses (separated by at least 4 weeks) to children aged younger than 9 years who are receiving influenza vaccine for the first time or who were vaccinated for the first time during the previous influenza season but only received 1 dose.
   - For recommendations for use of influenza A (H1N1) 2009 monovalent vaccine. See *MMWR* 2009;58(No. RR-10).
5. **Pneumococcal polysaccharide vaccine (PPSV).**
   - Administer to children with certain underlying medical conditions, including a cochlear implant. A single revaccination should be administered after 5 years to children with functional or anatomic asplenia or an immunocompromising condition. See *MMWR* 1997;46(No. RR-8).
6. **Hepatitis A vaccine (HepA).**
   - Administer 2 doses at least 6 months apart.
   - HepA is recommended for children aged older than 23 months who live in areas where vaccination programs target older children, who are at increased risk for infection, or for whom immunity against hepatitis A is desired.
7. **Hepatitis B vaccine (HepB).**
   - Administer the 3-dose series to those not previously vaccinated.
   - A 2-dose series (separated by at least 4 months) of adult formulation Recombivax HB is licensed for children aged 11 through 15 years.
8. **Inactivated poliovirus vaccine (IPV).**
   - The final dose in the series should be administered on or after the fourth birthday and at least 6 months following the previous dose.
   - If both OPV and IPV were administered as part of a series, a total of 4 doses should be administered, regardless of the child's current age.
9. **Measles, mumps, and rubella vaccine (MMR).**
   - If not previously vaccinated, administer 2 doses or the second dose for those who have received only 1 dose, with at least 28 days between doses.
10. **Varicella vaccine.**
    - For persons aged 7 through 18 years without evidence of immunity (see *MMWR* 2007;56[No. RR-4]), administer 2 doses if not previously vaccinated or the second dose if only 1 dose has been administered.
    - For persons aged 7 through 12 years, the minimum interval between doses is 3 months. However, if the second dose was administered at least 28 days after the first dose, it can be accepted as valid.
    - For persons aged 13 years and older, the minimum interval between doses is 28 days.

The Recommended Immunization Schedules for Persons Aged 0 through 18 Years are approved by the Advisory Committee on Immunization Practices (**http://www.cdc.gov/vaccines/recs/acip**), the American Academy of Pediatrics (**http://www.aap.org**), and the American Academy of Family Physicians (**http://www.aafp.org**).

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Catch-up Immunization Schedule for Persons Aged 4 Months Through 18 Years Who Start Late or Who Are More Than 1 Month Behind—United States • 2010

The table below provides catch-up schedules and minimum intervals between doses for children whose vaccinations have been delayed. A vaccine series does not need to be restarted, regardless of the time that has elapsed between doses. Use the section appropriate for the child's age.

Vaccine	Minimum Age for Dose 1	Minimum Interval Between Doses			
		Dose 1 to Dose 2	Dose 2 to Dose 3	Dose 3 to Dose 4	Dose 4 to Dose 5
PERSONS AGED 4 MONTHS THROUGH 6 YEARS					
Hepatitis B[1]	Birth	**4 weeks**	**8 weeks** (and at least 16 weeks after first dose)		
Rotavirus[2]	6 wks	**4 weeks**	**4 weeks**[2]		
Diphtheria, Tetanus, Pertussis[3]	6 wks	**4 weeks**	**4 weeks**	**6 months**	**6 months**[3]
Haemophilus influenzae type b[4]	6 wks	**4 weeks** if first dose administered at younger than age 12 months **8 weeks (as final dose)** if first dose administered at age 12–14 months **No further doses needed** if first dose administered at age 15 months or older	**4 weeks**[4] if current age is younger than 12 months **8 weeks (as final dose)**[4] if current age is 12 months or older and first dose administered at younger than age 12 months and second dose administered at younger than 15 months **No further doses needed** if previous dose administered at age 15 months or older	**8 weeks (as final dose)** This dose only necessary for children aged 12 months through 59 months who received 3 doses before age 12 months	
Pneumococcal[5]	6 wks	**4 weeks** if first dose administered at younger than age 12 months **8 weeks (as final dose for healthy children)** if first dose administered at age 12 months or older or current age 24 through 59 months **No further doses needed** for healthy children if first dose administered at age 24 months or older	**4 weeks** if current age is younger than 12 months **8 weeks (as final dose for healthy children)** if current age is 12 months or older **No further doses needed** for healthy children if previous dose administered at age 24 months or older	**8 weeks (as final dose)** This dose only necessary for children aged 12 months through 59 months who received 3 doses before age 12 months or for high-risk children who received 3 doses at any age	
Inactivated Poliovirus[6]	6 wks	**4 weeks**	**4 weeks**	**6 months**	
Measles, Mumps, Rubella[7]	12 mos	**4 weeks**			
Varicella[8]	12 mos	**3 months**			
Hepatitis A[9]	12 mos	**6 months**			
PERSONS AGED 7 THROUGH 18 YEARS					
Tetanus, Diphtheria/ Tetanus, Diphtheria, Pertussis[10]	7 yrs[10]	**4 weeks**	**4 weeks** if first dose administered at younger than age 12 months **6 months** if first dose administered at 12 months or older	**6 months** if first dose administered at younger than age 12 months	
Human Papillomavirus[11]	9 yrs	**Routine dosing intervals are recommended**[11]			
Hepatitis A[9]	12 mos	**6 months**			
Hepatitis B[1]	Birth	**4 weeks**	**8 weeks** (and at least 16 weeks after first dose)		
Inactivated Poliovirus[6]	6 wks	**4 weeks**	**4 weeks**	**6 months**	
Measles, Mumps, Rubella[7]	12 mos	**4 weeks**			
Varicella[8]	12 mos	**3 months** if person is younger than age 13 years **4 weeks** if person is aged 13 years or older			

1. **Hepatitis B vaccine (HepB).**
   - Administer the 3-dose series to those not previously vaccinated.
   - A 2-dose series (separated by at least 4 months) of adult formulation Recombivax HB is licensed for children aged 11 through 15 years.
2. **Rotavirus vaccine (RV).**
   - The maximum age for the first dose is 14 weeks 6 days. Vaccination should not be initiated for infants aged 15 weeks 0 days or older.
   - The maximum age for the final dose in the series is 8 months 0 days.
   - If Rotarix was administered for the first and second doses, a third dose is not indicated.
3. **Diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP).**
   - The fifth dose is not necessary if the fourth dose was administered at age 4 years or older.
4. ***Haemophilus influenzae* type b conjugate vaccine (Hib).**
   - Hib vaccine is not generally recommended for persons aged 5 years or older. No efficacy data are available on which to base a recommendation concerning use of Hib vaccine for older children and adults. However, studies suggest good immunogenicity in persons who have sickle cell disease, leukemia, or HIV infection, or who have had a splenectomy; administering 1 dose of Hib vaccine to these persons who have not previously received Hib vaccine is not contraindicated.
   - If the first 2 doses were PRP-OMP (PedvaxHIB or Comvax), and administered at age 11 months or younger, the third (and final) dose should be administered at age 12 through 15 months and at least 8 weeks after the second dose.
   - If the first dose was administered at age 7 through 11 months, administer the second dose at least 4 weeks later and a final dose at age 12 through 15 months.
5. **Pneumococcal vaccine.**
   - Administer 1 dose of pneumococcal conjugate vaccine (PCV) to all healthy children aged 24 through 59 months who have not received at least 1 dose of PCV on or after age 12 months.
   - For children aged 24 through 59 months with underlying medical conditions, administer 1 dose of PCV if 3 doses were received previously or administer 2 doses of PCV at least 8 weeks apart if fewer than 3 doses were received previously.
   - Administer pneumococcal polysaccharide vaccine (PPSV) to children aged 2 years or older with certain underlying medical conditions, including a cochlear implant, at least 8 weeks after the last dose of PCV. See *MMWR* 1997;46(No. RR-8).
6. **Inactivated poliovirus vaccine (IPV).**
   - The final dose in the series should be administered on or after the fourth birthday and at least 6 months following the previous dose.
   - A fourth dose is not necessary if the third dose was administered at age 4 years or older and at least 6 months following the previous dose.
   - In the first 6 months of life, minimum age and minimum intervals are only recommended if the person is at risk for imminent exposure to circulating poliovirus (i.e., travel to a polio-endemic region or during an outbreak).
7. **Measles, mumps, and rubella vaccine (MMR).**
   - Administer the second dose routinely at age 4 through 6 years. However, the second dose may be administered before age 4, provided at least 28 days have elapsed since the first dose.
   - If not previously vaccinated, administer 2 doses with at least 28 days between doses.
8. **Varicella vaccine.**
   - Administer the second dose routinely at age 4 through 6 years. However, the second dose may be administered before age 4, provided at least 3 months have elapsed since the first dose.
   - For persons aged 12 months through 12 years, the minimum interval between doses is 3 months. However, if the second dose was administered at least 28 days after the first dose, it can be accepted as valid.
   - For persons aged 13 years and older, the minimum interval between doses is 28 days.
9. **Hepatitis A vaccine (HepA).**
   - HepA is recommended for children aged older than 23 months who live in areas where vaccination programs target older children, who are at increased risk for infection, or for whom immunity against hepatitis A is desired.
10. **Tetanus and diphtheria toxoids vaccine (Td) and tetanus and diphtheria toxoids and acellular pertussis vaccine (Tdap).**
    - Doses of DTaP are counted as part of the Td/Tdap series
    - Tdap should be substituted for a single dose of Td in the catch-up series or as a booster for children aged 10 through 18 years; use Td for other doses.
11. **Human papillomavirus vaccine (HPV).**
    - Administer the series to females at age 13 through 18 years if not previously vaccinated.
    - Use recommended routine dosing intervals for series catch-up (i.e., the second and third doses should be administered at 1 to 2 and 6 months after the first dose). The minimum interval between the first and second doses is 4 weeks. The minimum interval between the second and third doses is 12 weeks, and the third dose should be administered at least 24 weeks after the first dose.

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Information about reporting reactions after immunization is available online at **http://www.vaers.hhs.gov** or by telephone, **800-822-7967.** Suspected cases of vaccine-preventable diseases should be reported to the state or local health department. Additional information, including precautions and contraindications for immunization, is available from the National Center for Immunization and Respiratory Diseases at **http://www.cdc.gov/vaccines** or telephone, **800-CDC-INFO** (800-232-4636).

Summary of Recommendations for Childhood and Adolescent Immunization

Vaccine name and route	Schedule for routine vaccination and other guidelines (any vaccine can be given with another)	Schedule for catch-up vaccination and related issues	Contraindications and precautions (mild illness is not a contraindication)
Hepatitis B (HepB) *Give IM*	• Vaccinate all children age 0 through 18yrs. • Vaccinate all newborns with monovalent vaccine prior to hospital discharge. Give dose #2 at age 1–2m and the final dose at age 6–18m (the last dose in the infant series should not be given earlier than age 24wks). After the birth dose, the series may be completed using 2 doses of single-antigen vaccine or up to 3 doses of Comvax (ages 2m, 4m, 12–15m) or Pediarix (ages 2m, 4m, 6m), which may result in giving a total of 4 doses of hepatitis B vaccine. • **If mother is HBsAg-positive:** give the newborn HBIG + dose #1 within 12hrs of birth; complete series at age 6m or, if using Comvax, at age 12–15m. • **If mother's HBsAg status is unknown:** give the newborn dose #1 within 12hrs of birth. If mother is subsequently found to be HBsAg positive, give infant HBIG within 7d of birth and follow the schedule for infants born to HBsAg-positive mothers.	• Do not restart series, no matter how long since previous dose. • 3-dose series can be started at any age. • Minimum intervals between doses: 4wks between #1 and #2, 8wks between #2 and #3, and at least 16wks between #1 and #3 (e.g., 0-, 2-, 4m; 0-, 1-, 4m). **Special Notes on Hepatitis B Vaccine (HepB)** **Dosing of HepB:** Monovalent vaccine brands are interchangeable. For people age 0 through 19yrs, give 0.5 mL of either Engerix-B or Recombivax HB. **Alternative dosing schedule for unvaccinated adolescents age 11 through 15yrs:** Give 2 doses Recombivax HB 1.0 mL (adult formulation) spaced 4–6m apart. (Engerix-B is not licensed for a 2-dose schedule.) **For preterm infants:** Consult ACIP hepatitis B recommendations (*MMWR* 2005; 54 [RR-16]).*	**Contraindication** Previous anaphylaxis to this vaccine or to any of its components. **Precaution** Moderate or severe acute illness.
DTaP, DT (Diphtheria, tetanus, acellular pertussis) *Give IM*	• Give to children at ages 2m, 4m, 6m, 15–18m, 4–6yrs. • May give dose #1 as early as age 6wks. • May give #4 as early as age 12m if 6m have elapsed since #3 and the child is unlikely to return at age 15–18m. • Do not give DTaP/DT to children age 7yrs and older. • If possible, use the same DTaP product for all doses.	• #2 and #3 may be given 4wks after previous dose. • #4 may be given 6m after #3. • If #4 is given before 4th birthday, wait at least 6m for #5 (age 4–6yrs). • If #4 is given after 4th birthday, #5 is not needed.	**Contraindications** • Previous anaphylaxis to this vaccine or to any of its components. • For DTaP/Tdap only: encephalopathy within 7d after DTP/DTaP. **Precautions** • Moderate or severe acute illness. • History of Arthus reaction following a prior dose of tetanus- and/or diphtheria-toxoid-containing vaccine, including MCV4. • Guillain-Barré syndrome (GBS) within 6wks after previous dose of tetanus-toxoid-containing vaccine. • For DTaP only: Any of these events following a previous dose of DTP/DTaP: 1) temperature of 105°F (40.5°C) or higher within 48hrs; 2) continuous crying for 3hrs or more within 48hrs; 3) collapse or shock-like state within 48hrs; 4) convulsion with or without fever within 3d. • For DTaP/Tdap only: Unstable neurologic disorder. • For Td in teens: Progressive neurologic disorder. **Note:** Tdap may be given to pregnant women at the provider's discretion.
Td, Tdap (Tetanus, diphtheria, acellular pertussis) *Give IM*	• Give 1-time Tdap dose to adolescents age 11–12yrs if 5yrs have elapsed since last dose DTaP; then boost every 10yrs with Td. • Give 1-time dose of Tdap to all adolescents who have not received previous Tdap. Special efforts should be made to give Tdap to people age 11yrs and older who are 1) in contact with infants younger than age 12m and 2) healthcare workers with direct patient contact. • In pregnancy, when indicated, give Td or Tdap in 2nd or 3rd trimester. If not administered during pregnancy, give Tdap in immediate postpartum period.	• If never vaccinated with tetanus- and diphtheria-containing vaccine: give Td dose #1 now, dose #2 4wks later, and dose #3 6m after #2, then give booster every 10yrs. A 1-time Tdap may be substituted for any dose in the series, preferably as dose #1. If previously received Td booster, an interval of 2yrs or less between Td and Tdap may be used.	
Polio (IPV) *Give SC or IM*	• Give to children at ages 2m, 4m, 6–18m, 4–6yrs. • May give dose #1 as early as age 6wks. • Not routinely recommended for U.S. residents age 18yrs and older (except certain travelers).	• The final dose should be given on or after the 4th birthday and at least 6m from the previous dose. • If dose #3 is given after 4th birthday, dose #4 is not needed if dose #3 is given at least 6m after dose #2.	**Contraindication** Previous anaphylaxis to this vaccine or to any of its components. **Precautions** • Moderate or severe acute illness. • Pregnancy.

*This document was adapted from the recommendations of the Advisory Committee on Immunization Practices (ACIP). To obtain copies of the recommendations, call the CDC-INFO Contact Center at (800) 232-4636; visit CDC's website at www.cdc.gov/vaccines/pubs/ACIP-list.htm; or visit the Immunization Action Coalition (IAC) website at www.immunize.org/acip. This table is revised periodically. Visit IAC's website at www.immunize.org/childrules to make sure you have the most current version.

Technical content reviewed by the Centers for Disease Control and Prevention, April 2010.

www.immunize.org/catg.d/p2010.pdf • Item #P2010 (4/10)

Summary of Recommendations for Childhood and Adolescent Immunization

Vaccine name and route	Schedule for routine vaccination and other guidelines (any vaccine can be given with another)	Schedule for catch-up vaccination and related issues	Contraindications and precautions (mild illness is not a contraindication)
Seasonal Influenza Trivalent inactivated influenza vaccine (TIV) *Give IM* Live attenuated influenza vaccine (LAIV) *Give intranasally*	• Vaccinate all children and teens age 6m through 18yrs. • LAIV may be given to healthy, non-pregnant people age 2–49yrs. • Give 2 doses to first-time vaccinees age 6m through 8yrs, spaced 4wks apart. • For TIV, give 0.25 mL dose to children age 6–35m and 0.5 mL dose if age 3yrs and older.		**Contraindications** • Previous anaphylaxis to this vaccine, to any of its components, or to eggs. • For LAIV only: age younger than 2yrs; pregnancy; chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, neurological/neuromuscular, hematologic, or metabolic (including diabetes) disorders; immunosuppression (including that caused by medications or HIV); for children and teens ages 6m through 18yrs, current long-term aspirin therapy; for children age 2 through 4yrs, wheezing or asthma within the past 12m, per healthcare provider statement. **Precautions** • Moderate or severe acute illness. • History of Guillain-Barré syndrome (GBS) within 6wks of a previous influenza vaccination. • For LAIV only: - Close contact with an immunosuppressed person when the person requires protective isolation. - Receipt of specific antivirals (i.e., amantadine, rimantadine, zanamivir, or oseltamivir) 48hrs before vaccination. Avoid use of these antiviral drugs for 14d after vaccination.
Varicella (Var) (Chickenpox) *Give SC*	• Give dose #1 at age 12–15m. • Give dose #2 at age 4–6yrs. Dose #2 may be given earlier if at least 3m since dose #1. • Give a 2nd dose to all older children and adolescents with history of only 1 dose. • MMRV may be used in children age 12m through 12yrs. • MMRV generally is preferred over separate injections of its separate components in children receiving their first dose at ages 4 through 12yrs or their second dose at any age through 12yrs.	• If younger than age 13yrs, space dose #1 and #2 at least 3m apart. If age 13yrs or older, space at least 4wks apart. • May use as postexposure prophylaxis if given within 5d. • If Var and either MMR, LAIV, and/or yellow fever vaccine are not given on the same day, space them at least 28d apart.	**Contraindications** • Previous anaphylaxis to this vaccine or to any of its components. • Pregnancy or possibility of pregnancy within 4wks. • Children on high-dose immunosuppressive therapy or who are immunocompromised because of malignancy and primary or acquired cellular immunodeficiency, including HIV/AIDS (although vaccination may be considered if CD4+ T-lymphocyte percentages are either 15% or greater in children ages 1 through 8yrs or 200 cells/μL or greater in children age 9yrs and older). **Precautions** • Moderate or severe acute illness. • If blood, plasma, and/or immune globulin (IG or VZIG) were given in past 11m, see ACIP statement *General Recommendations on Immunization** regarding time to wait before vaccinating. • Receipt of specific antivirals (i.e., acyclovir, famciclovir, or valacyclovir) 24hrs before vaccination, if possible; delay resumption of these antiviral drugs for 14d after vaccination. • For MMRV only, personal or family (i.e., sibling or parent) history of seizures. **Note:** For patients with humoral immunodeficiency or leukemia, see ACIP recommendations*.
MMR (Measles, mumps, rubella) *Give SC*	• Give dose #1 at age 12–15m. • Give dose #2 at age 4–6yrs. Dose #2 may be given earlier if at least 4wks since dose #1. • Give a 2nd dose to all older children and teens with history of only 1 dose. • MMRV may be used in children age 12m through 12yrs. • MMRV generally is preferred over separate injections of its separate components in children receiving their first dose at ages 4 though 12yrs or their second dose at any age through 12yrs.	• If MMR and either Var, LAIV, and/or yellow fever vaccine are not given on the same day, space them at least 28d apart. • When using MMR for both doses, minimum interval is 4wks. • When using MMRV for both doses, minimum interval is 3m. • Within 72hrs of measles exposure, give 1 dose of MMR as postexposure prophylaxis to susceptible healthy children age 12m and older.	**Contraindications** • Previous anaphylaxis to this vaccine or to any of its components. • Pregnancy or possibility of pregnancy within 4wks. • Severe immunodeficiency (e.g., hematologic and solid tumors; receiving chemotherapy; congenital immunodeficiency; long-term immunosuppressive therapy, or severely symptomatic HIV). Note: HIV infection is NOT a contraindication to MMR for children who are not severely immunocompromised (consult ACIP MMR recommendations [*MMWR* 1998;47 [RR-8] for details*). **Precautions** • Moderate or severe acute illness. • If blood, plasma, or immune globulin given in past 11m, see ACIP statement *General Recommendations on Immunization** regarding time to wait before vaccinating. • History of thrombocytopenia or thrombocytopenic purpura. • For MMRV only, personal or family (i.e., sibling or parent) history of seizures. **Note:** MMR is not contraindicated if a TST (tuberculosis skin test) was recently applied. If TST and MMR are not given on same day, delay TST for at least 4wks after MMR.

Summary of Recommendations for Childhood and Adolescent Immunization

Vaccine name and route	Schedule for routine vaccination and other guidelines (any vaccine can be given with another)	Schedule for catch-up vaccination and related issues	Contraindications and precautions (mild illness is not a contraindication)
Hib (*Haemophilus influenzae* type b) *Give IM*	• ActHib (PRP-T): give at age 2m, 4m, 6m, 12–15m (booster dose). • PedvaxHIB or Comvax (containing PRP-OMP): give at age 2m, 4m, 12–15m (booster dose). • Dose #1 of Hib vaccine should not be given earlier than age 6wks. • The last dose (booster dose) is given no earlier than age 12m and a minimum of 8wks after the previous dose. • Hib vaccines are interchangeable; however, if different brands of Hib vaccines are administered for dose #1 and dose #2, a total of 3 doses are necessary to complete the primary series in infants. • Any Hib vaccine may be used for the booster dose. • Hib is not routinely given to children age 5yrs and older. • Hiberix is approved ONLY for the booster dose at age 15m through 4yrs.	**All Hib vaccines:** • If #1 was given at 12–14m, give booster in 8wks. • Give only 1 dose to unvaccinated children ages 15 through 59m. **ActHib:** • #2 and #3 may be given 4wks after previous dose. • If #1 was given at age 7–11m, only 3 doses are needed; #2 is given 4–8wks after #1, then boost at age 12–15m (wait at least 8wks after dose #2). **PedvaxHIB and Comvax:** • #2 may be given 4wks after dose #1.	**Contraindications** • Previous anaphylaxis to this vaccine or to any of its components. • Age younger than 6wks. **Precaution** Moderate or severe acute illness.
Pneumococcal conjugate (PCV13) *Give IM*	As soon as feasible, replace existing stock of PCV7 with PCV13. • Give at ages 2m, 4m, 6m, 12–15m. • Dose #1 may be given as early as age 6wks. • When children are behind on PCV schedule, minimum interval for doses given to children younger than age 12m is 4wks; for doses given at 12m and older is 8wks. • Give 1 dose to unvaccinated healthy children age 24–59m. • For high-risk** children ages 24–71m: Give 2 doses at least 8wks apart if they previously received fewer than 3 doses; give 1 dose at least 8wks after the most recent dose if they previously received 3 doses. • PCV13 is not routinely given to healthy children age 5yrs and older.	• For minimum intervals, see bullet #3 at left. • For age 7–11m: If history of 0 doses, give 2 doses 4wks apart, with a 3rd dose at age 12–15m; if history of 1 or 2 doses, give 1 dose with a 2nd dose at age 12–15m. • For age 12–23m: If unvaccinated or history of 1 dose before age 12m, give 2 doses 8wks apart; if history of 1 dose at or after age 12m or 2 or 3 doses before age 12m, give 1 dose at least 8wks after most recent dose. • For age 24–59m and healthy: If unvaccinated or any incomplete schedule or if 4 doses of PCV7 or any other age-appropriate complete PCV7 schedule, give 1 dose at least 8wks after the most recent dose. • For age 24–71m and at high risk**: If unvaccinated or any incomplete schedule of 1 or 2 doses, give 2 doses, 1 at least 8wks after the most recent dose and another dose at least 8wks later; if any incomplete series of 3 doses, or if 4 doses of PCV7 or any other age-appropriate complete PCV7 schedule, give 1 dose at least 8wks after the most recent dose. • For children ages 6 through 18yrs with functional or anatomic asplenia (including sickle cell disease), HIV infection or other immunocompromising condition, cochlear implant, or CSF leak, consider giving 1 dose of PCV13 regardless of previous history of PCV7 or PPSV.	**Contraindication** Previous anaphylaxis to a PCV vaccine, to any of its components, or to any diphtheria toxoid-containing vaccine. **Precaution** Moderate or severe acute illness.
Pneumococcal polysaccharide (PPSV) *Give IM or SC*	****High-risk:** Those with sickle cell disease; anatomic or functional asplenia; chronic cardiac, pulmonary, or renal disease; diabetes; cerebrospinal fluid leaks; HIV infection; immunosuppression; diseases associated with immunosuppressive and/or radiation therapy; or who have or will have a cochlear implant. • Give 1 dose at least 8wks after final dose of PCV to high-risk children age 2yrs and older. • For children who are immunocompromised or have sickle cell disease or functional or anatomic asplenia, give a 2nd dose of PPSV 5yrs after previous PPSV (consult ACIP PPSV recommendations at www.cdc.gov/vaccines/pubs/ACIP-list.htm*).		**Contraindication** Previous anaphylaxis to this vaccine or to any of its components. **Precaution** Moderate or severe acute illness.

Summary of Recommendations for Childhood and Adolescent Immunization

Vaccine name and route	Schedule for routine vaccination and other guidelines (any vaccine can be given with another)	Schedule for catch-up vaccination and related issues	Contraindications and precautions (mild illness is not a contraindication)
Rotavirus (RV) *Give orally*	• Rotarix (RV1): give at age 2m, 4m. • RotaTeq (RV5): give at age 2m, 4m, 6m. • May give dose #1 as early as age 6wks. • Give final dose no later than age 8m 0 days.	• Do not begin series in infants older than age 15wks 0 days. • Intervals between doses may be as short as 4wks. • If prior vaccination included use of different or unknown brand(s), a total of 3 doses should be given.	**Contraindication** Previous anaphylaxis to this vaccine or to any of its components. If allergy to latex, use RV5. **Precautions** • Moderate or severe acute illness. • Altered immunocompetence. • Moderate to severe acute gastroenteritis or chronic pre-existing gastrointestinal disease. • History of intussusception.
Hepatitis A (HepA) *Give IM*	• Give 2 doses spaced 6m apart to all children at age 1yr (12–23m). • Vaccinate all previously unvaccinated children and adolescents age 2yrs and older who - Want to be protected from HAV infection. - Live in areas where vaccination programs target older children. - Travel anywhere except U.S., W. Europe, N. Zealand, Australia, Canada, or Japan. - Have chronic liver disease, clotting factor disorder, or are adolescent males who have sex with other males. - Are users of illicit drugs (injectable or non-injectable). - Anticipate close personal contact with an international adoptee from a country of high or intermediate endemicity during the first 60 days following the adoptee's arrival in the U.S.	• Minimum interval between doses is 6m. • Children who are not fully vaccinated by age 2yrs can be vaccinated at subsequent visits. • Consider routine vaccination of children age 2yrs and older in areas with no existing program. • Give 1 dose as postexposure prophylaxis to incompletely vaccinated children age 12m and older who have recently (during the past 2wks) been exposed to hepatitis A virus.	**Contraindication** Previous anaphylaxis to this vaccine or to any of its components. **Precautions** • Moderate or severe acute illness. • Pregnancy.
Meningococcal conjugate (MCV4) Menactra (ages 2–55yrs) Menveo (ages 11–55yrs) *Give IM* —— **Meningococcal polysaccharide** (MPSV4) *Give SC*	• Give 1-time dose of MCV4 to adolescents age 11 through 18yrs. • Vaccinate all college freshmen living in dorms who have not been vaccinated. • Vaccinate all children age 2yrs and older who have any of the following risk factors: - Anatomic or functional asplenia, or persistent complement component deficiency. - Travel to or reside in countries in which meningococcal disease is hyperendemic or epidemic (e.g., the "meningitis belt" of Sub-Saharan Africa). - Military recruits **Note:** Use MPSV4 ONLY if there is a permanent contraindication or precaution to MCV4.	If previously vaccinated with MPSV4 or MCV4 and risk of meningococcal disease persists, revaccinate with Menactra in 3yrs (if first dose given at age 2 through 6yrs) or revaccinate with either brand of MCV4 after 5yrs (if previous dose given at age 7yrs or older). If the only risk factor is living in a campus dormitory, there is no need to give a 2nd dose if previous dose was MCV4.	**Contraindication** Previous anaphylaxis to any any meningococcal vaccine or to any of its components, including diphtheria toxoid (for MCV4). **Precautions** • Moderate or severe acute illness. • For MCV4 only: history of Guillain-Barré syndrome (if not at extremely high risk for meningococcal disease). • In pregnancy, studies of vaccination with MPSV4 have not documented adverse effects so may use MPSV4 if indicated. No data are available on the safety of MCV4 during pregnancy.
Human papillomavirus HPV (HPV2, Cervarix) (HPV4, Gardasil) *Give IM*	• Give 3-dose series to girls at age 11–12yrs on a 0, 1–2, 6m schedule. (May be given as early as age 9yrs.) • Vaccinate all older girls and women (through age 26yrs) who were not previously vaccinated. • Consider giving HPV4 to males age 9 through 26yrs to reduce their likelihood of acquiring genital warts.	Minimum intervals between doses: 4wks between #1 and #2; 12 wks between #2 and #3. Overall, there must be at least 24wks between doses #1 and #3. If possible, use the same vaccine product for all doses.	**Contraindication** Previous anaphylaxis to this vaccine or to any of its components. **Precautions** • Moderate or severe acute illness. • Pregnancy.

Please note: *Errata have been published for this article. To view the errata, please click here and here.*

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General Recommendations on Immunization

Recommendations of the Advisory Committee on Immunization Practices (ACIP)



INSIDE: Continuing Education Examination

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

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Disclosure of Relationship

CDC, our planners, and our presenters wish to disclose they have no financial interests or other relationships with the manufacturers of commercial products, suppliers of commercial services, or commercial supporters.

This report will not include any discussion of the unlabeled use of a product or a product under investigational use with the exception of the discussion of:

1. The nonsimultaneous administration of yellow fever vaccine and inactivated vaccines.
2. Progressive neurologic disorders are a precaution for the use of tetanus-reduced diphtheria acellular pertussis vaccine for adolescents and adults.
3. Contact allergy to latex is neither a contraindication nor a precaution to the use of meningococcal vaccine in the absence of an anaphylactic allergy.
4. Meningococcal conjugate vaccine should be administered intramuscularly, but if administered subcutaneously, repeating the dose is unnecssary.
5. Use of immune globulin, intravenous for postexposure prophylaxis or varicella.
6. Use of VariZIG for postexposure prophylaxis of varicella (unlicensed).

General Recommendations on Immunization

Recommendations of the Advisory Committee on Immunization Practices (ACIP)

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Summary

This report is a revision of General Recommendations on Immunization and updates the 2002 statement by the Advisory Committee on Immunization Practices (ACIP) (CDC. General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices and the American Academy of Family Physicians. MMWR 2002;51[No. RR-2]). This report is intended to serve as a general reference on vaccines and immunization. The principal changes include 1) expansion of the discussion of vaccination spacing and timing; 2) an increased emphasis on the importance of injection technique/age/body mass in determining appropriate needle length; 3) expansion of the discussion of storage and handling of vaccines, with a table defining the appropriate storage temperature range for inactivated and live vaccines; 4) expansion of the discussion of altered immunocompetence, including new recommendations about use of live-attenuated vaccines with therapeutic monoclonal antibodies; and 5) minor changes to the recommendations about vaccination during pregnancy and vaccination of internationally adopted children, in accordance with new ACIP vaccine-specific recommendations for use of inactivated influenza vaccine and hepatitis B vaccine. The most recent ACIP recommendations for each specific vaccine should be consulted for comprehensive discussion. This report, ACIP recommendations for each vaccine, and other information about vaccination can be accessed at CDC's National Center for Immunization and Respiratory Diseases (proposed) (formerly known as the National Immunization Program) website at http//:www.cdc.gov/nip.

Introduction

This report provides technical guidance about common vaccination concerns for clinicians and other health-care providers who administer vaccines to infants, children, adolescents, and adults. Vaccine recommendations are based on characteristics of the immunobiologic product, scientific knowledge about the principles of active and passive immunization, epidemiology and burden of diseases (i.e., morbidity, mortality, costs of treatment, and loss of productivity), vaccine safety considerations, cost analysis of preventive measures, published and unpublished studies, and expert opinion of public health officials and specialists in clinical and preventive medicine.

The material in this report was prepared for publication by the National Center for Immunization and Respiratory Diseases, Anne Schuchat, MD, Director; and the Immunization Services Division, Lance E. Rodewald, MD, Director.
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Benefits and risks are associated with using all immunobiologics (i.e., an antigenic substance or antibody-containing preparation). No vaccine is completely safe or effective. Benefits of vaccination include partial or complete protection against infection for the vaccinated person and overall benefits to society as a whole. Benefits include protection from symptomatic illness, improved quality of life and productivity, and prevention of death. Societal benefits include creation and maintenance of herd immunity against communicable diseases, prevention of disease outbreaks, and reduction in health-care–related costs. Vaccination risks range from common, minor, and local adverse effects to rare, severe, and life-threatening conditions. Therefore, recommendations for vaccination practices balance scientific evidence of benefits for each person and to society against the potential costs and risks for vaccination for the individual and programs.

Standards for child and adolescent vaccination practices and standards for adult vaccination practices (*1,2*) have been published to assist with implementing vaccination programs and maximizing their benefits. Any person or institution that provides vaccination services should adopt these standards to improve vaccination delivery and protect infants, children, adolescents, and adults from vaccine-preventable diseases.

To maximize the benefits of vaccination, this report provides general information about immunobiologics and provides practical guidelines about vaccine administration and technique. To minimize risk from vaccine administration, this report delineates situations that warrant precautions or contraindications to using a vaccine. These recommendations are intended for use in the United States because vaccine availability and use and epidemiologic circumstances differ in other countries. Individual circumstances might warrant deviations from these recommendations.

The relative balance of benefits and risks can change as diseases are controlled or eradicated. For example, because wild poliovirus transmission has been interrupted in the United States since 1979, the only indigenous cases of paralytic poliomyelitis reported since that time have been caused by live oral poliovirus vaccine (OPV) (*3*). In 1999, to eliminate the risk for vaccine-associated paralytic poliomyelitis (VAPP), exclusive use of inactivated poliovirus vaccine (IPV) was recommended for routine vaccination in the United States. However, because of superior ability to induce intestinal immunity and to prevent spread among close contacts, OPV remains the vaccine of choice for areas where wild poliovirus is still present (*4*). Until worldwide eradication of poliovirus is accomplished, continued vaccination of the U.S. population against poliovirus will be necessary.

Timing and Spacing of Immunobiologics

General Principles for Vaccine Scheduling

Optimal response to a vaccine depends on multiple factors, including the nature of the vaccine and the age and immune status of the recipient. Recommendations for the age at which vaccines are administered are influenced by age-specific risks for disease, age-specific risks for complications, ability of persons of a certain age to respond to the vaccine, and potential interference with the immune response by passively transferred maternal antibody. Vaccines are recommended for members of the youngest age group at risk for experiencing the disease for whom efficacy and safety have been demonstrated.

Certain products, including inactivated vaccines, toxoids, recombinant subunit, and polysaccharide conjugate vaccines, require administering 2 or more doses for development of an adequate and persisting antibody response. Tetanus and diphtheria toxoids require periodic reinforcement or booster doses to maintain protective antibody concentrations. Unconjugated polysaccharide vaccines do not induce T-cell memory, and booster doses are not expected to produce substantially increased protection. Conjugation with a protein carrier improves the effectiveness of polysaccharide vaccines by inducing T-cell–dependent immunologic function. Vaccines that stimulate both cell-mediated immunity and neutralizing antibodies (e.g., live-attenuated virus vaccines) usually can induce prolonged immunity, even if antibody titers decline over time (*5*). Subsequent exposure to infection usually does not lead to viremia but to a rapid anamnestic antibody response.

Approximately 90%–95% of recipients of a single dose of certain live vaccines administered by injection at the recommended age (i.e., measles, rubella, and yellow fever) have protective antibody (generally within 2 weeks of the dose). For varicella and mumps vaccines, 80%–85% of vaccinees are protected after a single dose. However, because a limited proportion of recipients (5%–15%) of measles-mumps-rubella (MMR) or varicella vaccine fail to respond to 1 dose, a second dose is recommended to provide another opportunity to develop immunity (*6*). The majority of persons who fail to respond to the first dose of MMR or varicella vaccine respond to a second dose (*7,8*).

The Recommended Childhood and Adolescent Immunization Schedule and the Recommended Adult Immunization Schedule are revised annually. Physicians and other healthcare providers should ensure that they are following the most up-to-date schedules, which are available from CDC's National Center for Immunization and Respiratory Diseases (proposed) website (http://www.cdc.gov/nip).

Spacing of Multiple Doses of the Same Antigen

Vaccination providers should adhere as closely as possible to recommended vaccination schedules. Recommended ages and intervals between doses of multidose antigens provide optimal protection or have the best evidence of efficacy. Recommended vaccines and recommended intervals between doses are provided in this report (Table 1).

In certain circumstances, administering doses of a multidose vaccine at shorter than the recommended intervals might be necessary. This can occur when a person is behind schedule and needs to be brought up-to-date as quickly as possible or when international travel is impending. In these situations, an accelerated schedule can be implemented that uses intervals between doses shorter than those recommended for routine vaccination. Although the effectiveness of all accelerated schedules has not been evaluated in clinical trials, ACIP believes that when accelerated intervals are used, the immune response is acceptable and will lead to adequate protection. The accelerated or minimum intervals and ages that can be used for scheduling catch-up vaccinations are provided in this report (Table 1). Vaccine doses should not be administered at

TABLE 1. Recommended and minimum ages and intervals between vaccine doses of routinely recommended vaccines*

Vaccine and dose no.	Recommended age for this dose	Minimum age for this dose	Recommended interval to next dose	Minimum interval to next dose
Hepatitis B (HepB)-1†	Birth	Birth	1–4 months	4 weeks
HepB-2	1–2 months	4 weeks	2–17 months	8 weeks
HepB-3§	6–18 months	24 weeks	—	—
Diphtheria-tetanus-acellular pertussis (DTaP)-1†	2 months	6 weeks	2 months	4 weeks
DTaP-2	4 months	10 weeks	2 months	4 weeks
DTaP-3	6 months	14 weeks	6–12 months¶	6 months¶**
DTaP-4	15–18 months	12 months	3 years	6 months¶
DTaP-5	4–6 years	4 years	—	—
Haemophilus influenzae type b (Hib)-1†,††	2 months	6 weeks	2 months	4 weeks
Hib-2	4 months	10 weeks	2 months	4 weeks
Hib-3§§	6 months	14 weeks	6–9 months¶	8 weeks
Hib-4	12–15 months	12 months	—	—
Inactivated poliovirus (IPV)-1†	2 months	6 weeks	2 months	4 weeks
IPV-2	4 months	10 weeks	2–14 months	4 weeks
IPV-3	6–18 months	14 weeks	3–5 years	4 weeks
IPV-4	4–6 years	18 weeks	—	—
Pneumococcal conjugate (PCV)-1††	2 months	6 weeks	2 months	4 weeks
PCV-2	4 months	10 weeks	2 months	4 weeks
PCV-3	6 months	14 weeks	6 months	8 weeks
PCV-4	12-15 months	12 months	—	—
Measles-mumps-rubella (MMR)-1¶¶	12–15 months	12 months	3–5 years	4 weeks
MMR-2¶¶	4–6 years	13 months	—	—
Varicella (Var)-1¶¶	12–15 months	12 months	3–5 years	12 weeks***
Var-2¶¶	4–6 years	15 months	—	—
Hepatitis A (HepA)-1†	12-23 months	12 months	6–18 months¶	6 months¶
HepA-2	18–41 months	18 months	—	—
Influenza inactivated†††	6-59 months	6 months§§§	1 month	4 weeks
Influenza live attenuated†††	—	5 years	6–10 weeks	6 weeks
Meningococcal conjugate†	11–12 years	11 years	—	—
Meningococcal polysaccharide (MPSV)-1	—	2 years	5 years§§§	5 years¶¶¶
MPSV-2****	—	7 years	—	—
Tetanus-diphtheria	11–12 years	7 years	10 years	5 years
Tetanus-diphtheria acellular pertussis (Tdap)††††	≥11 years	10 years	—	—
Pneumococcal polysaccharide (PPV)-1	—	2 years	5 years	5 years
PPV-2§§§§	—	7 years	—	—
Human papillomavirus (HPV)-1¶¶¶¶	11–12 years	9 years	2 months	4 weeks
HPV-2	11–12 years (+2 months)	109 months	4 months	12 weeks
HPV-3	11–12 years (+6 months)	112 months	—	—
Rotavirus (RV)-1*****	2 months	6 weeks	2 months	4 weeks
RV-2	4 months	10 weeks	2 months	4 weeks
RV-3	6 months	14 weeks	—	—
Zoster†††††	60 years	60 years	—	

* Combination vaccines are available. Use of licensed combination vaccines is preferred over separate injections of their equivalent component vaccines (**Source:** CDC. Combination vaccines for childhood immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics (AAP), and the American Academy of Family Physicians (AAFP). MMWR 1999;48[No. RR-5]). When administering combination vaccines, the minimum age for administration is the oldest age for any of the individual components; the minimum interval between doses is equal to the greatest interval of any of the individual components.

TABLE 1. (*Continued*) Recommended and minimum ages and intervals between vaccine doses of routinely recommended vaccines*

Vaccine and dose no.	Recommended age for this dose	Minimum age for this dose	Recommended interval to next dose	Minimum interval to next dose

† Combination vaccines containing the Hepatitis B component are available (HepB-Hib, DTaP-HepB-IPV, and HepA-HepB). These vaccines should not be administered to infants aged <6 weeks because of the other components (i.e., Hib, DTaP, HepA, and IPV).
§ HepB-3 should be administered at least 8 weeks after HepB-2 and at least 16 weeks after HepB-1 and should not be administered before age 24 weeks.
¶ Calendar months.
** The minimum recommended interval between DTaP-3 and DTaP-4 is 6 months. However, DTaP-4 need not be repeated if administered at least 4 months after DTaP-3.
†† For Hib and PCV, children receiving the first dose of vaccine at age ≥7 months require fewer doses to complete the series (CDC. Recommended childhood and adolescent immunization schedule—United States, 2006. MMWR 2005; 54 [Nos. 51 & 52]:Q1-Q4).
§§ If PRP-OMP (Pedvax-Hib®, Merck Vaccine Division) was administered at age 2 and 4 months, a dose at age 6 months is not required.
¶¶ Combination measles-mumps-rubella-varicella (MMRV) vaccine can be used for children aged 12 months–12 years.
*** The minimum interval from VAR-1 to VAR-2 for persons beginning the series at age ≥13 years is 4 weeks.
††† Two doses of influenza vaccine are recommended for children aged <9 years who are receiving the vaccine for the first time. Children aged <9 years who have previously received influenza vaccine, and persons aged ≥9 years require only 1 dose per influenza season.
§§§ The minimum age for inactivated influenza vaccine varies by vaccine manufacturer. Only Fluzone (manufactured by sanofi pasteur) is approved for children aged 6–35 months. The minimum age for Fluvirin (manufactured by Novartis) is 4 years. For Fluarix and FluLeval (manufactured by GlaxoSmithKline), the minimum age is 18 years.
¶¶¶ Certain experts recommend a second dose of MPSV 3 years after the first dose for persons at increased risk for meningococcal disease.
**** A second dose of meningococcal vaccine is recommended for persons previously vaccinated with MPSV who remain at high risk for meningococcal disease. MCV4 is preferred when revaccinating persons aged 11–55 years, but a second dose of MPSV is acceptable. (**Source:** CDC. Prevention and control of meningococcal disease: recommendations of the Advisory Committee on Immunization Practices [ACIP]. MMWR 2005;54[No. RR-7]).
†††† Only 1 dose of Tdap is recommended. Subsequent doses should be administered as Td. If vaccination to prevent tetanus and/or diphtheria disease is required for children aged 7–9 years, Td should be administered (minimum age for Td is 7 years). For one brand of Tdap, the minimum age is 11 years. The preferred interval between Tdap and a previous dose of Td is 5 years. In persons who have received a primary series of tetanus-toxoid–containing vaccine, for management of a tetanus-prone wound, the minimum interval after a previous dose of any tetanus-containing vaccine is 5 years.
§§§§ A second dose of PPV is recommended for persons at highest risk for serious pneumococcal infection and those who are likely to have a rapid decline in pneumococcal antibody concentration. Revaccination 3 years after the previous dose can be considered for children at highest risk for severe pneumococcal infection who would be aged <10 years of age at the time of revaccination. (**Source:** CDC. Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunization Practices [ACIP]. MMWR 1997;46[No. RR-8]).
¶¶¶¶ HPV is approved only for females aged 9–26 years.
***** The first dose of RV must be administered at age 6–12 weeks. The vaccine series should not be started at age ≥13 weeks. RV should not be administered to children aged ≥33 weeks regardless of the number of doses received at age 6–32 weeks.
†††††Herpes zoster vaccine is approved as a single dose for persons who are aged ≥60 years with a history of varicella.

intervals less than these minimum intervals or earlier than the minimum age.*

In clinical practice, vaccine doses occasionally are administered at intervals less than the minimum interval or at ages younger than the minimum age. Doses administered too close together or at too young an age can lead to a suboptimal immune response. However, administering a dose a limited number of days earlier than the minimum interval or age is unlikely to have a substantially negative effect on the immune response to that dose. Therefore, ACIP recommends that vaccine doses administered 4 or fewer days before the minimum interval or age be counted as valid.† However, because of its unique schedule, this recommendation does not apply to the rabies vaccine (*9*). Doses administered 5 or more days earlier than the minimum interval or age of any vaccine should not be counted as valid doses and should be repeated as age-appropriate. The repeat dose should be spaced after the invalid dose by the recommended minimum interval (Table 1). For example, if *Haemophilus influenzae* type b (Hib) doses one and two were administered only 2 weeks apart, because the minimum interval from dose one to dose two is 4 weeks, dose two is invalid and should be repeated. The repeat dose should be administered 4 or more weeks after the invalid (second) dose. The repeat dose would be counted as the second valid dose. Doses administered 5 or more days before the minimum age should be repeated on or after the child reaches the minimum age and 4 or more weeks after the invalid dose. For example, if the first dose of varicella vaccine were administered at age 10 months, the repeat dose would be administered no earlier than the child's first birthday. If the first dose of varicella vaccine were administered at age 11 months and 2 weeks, the repeat dose could be administered 2 weeks after the first birthday.

Certain vaccines produce increased rates of local or systemic reactions in certain recipients when administered too frequently (e.g., adult tetanus-diphtheria toxoid [Td]; pedi-

*During measles outbreaks, if cases are occurring among infants aged <12 months, measles vaccination of infants as young as 6 months can be undertaken as an outbreak control measure. However, doses administered at ages <12 months should not be counted as part of the series (**Source**: CDC. Measles, mumps, and rubella vaccine use and strategies for elimination of measles, rubella, and congenital rubella syndrome and control of mumps: recommendations of the Advisory Committee on Immunization Practices [ACIP]. MMWR 1998;47[No. RR-8]).

†In certain situations, local or state requirements might mandate that doses of selected vaccines be administered on or after specific ages. For example, a school entry requirement might not accept a dose of MMR or varicella vaccine administered before the child's first birthday. ACIP recommends that physicians and other health-care providers comply with local or state vaccination requirements when scheduling and administering vaccines.

atric diphtheria-tetanus toxoid [DT]; tetanus toxoid; and tetanus, reduced diphtheria acellular pertussis vaccine for adolescents and adults) (*10,11*). Such reactions might result from formation of antigen-antibody complexes. Optimal record keeping, maintaining patient histories, and adhering to recommended schedules can decrease the incidence of such reactions without adversely affecting immunity.

Simultaneous Administration

Experimental evidence and extensive clinical experience provide the scientific basis for administering vaccines simultaneously (i.e., during the same office visit, not combined in the same syringe). Simultaneously administering all vaccines for which a person is eligible is critical, including for childhood vaccination programs, because simultaneous administration increases the probability that a child will be vaccinated fully at the appropriate age (*1*). A study conducted during a measles outbreak demonstrated that approximately one third of measles cases among unvaccinated but vaccine-eligible preschool children could have been prevented if MMR had been administered at the same visit when another vaccine was administered (*12*). Simultaneous administration also is critical when preparing for foreign travel and/or if uncertainty exists that a person will return for further doses of vaccine.

Simultaneously administering the most widely used live and inactivated vaccines have produced seroconversion rates and rates for adverse reactions similar to those observed when the vaccines are administered separately (*13–16*). Routinely administering all age-appropriate doses of vaccines simultaneously is recommended for children for whom no specific contraindications exist at the time of the visit. Administering combined MMR (or measles-mumps-rubella-varicella [MMRV] vaccine) yields safety and immunogenicity results similar to administering individual measles, mumps, and rubella vaccines at different sites. Therefore, no medical basis exists for administering these vaccines separately for routine vaccination instead of the preferred MMR combined vaccine (*6*). Administering separate antigens would result in a delay in protection for the deferred components. Response to MMR and varicella vaccines administered on the same day is identical to vaccines administered a month apart (*17*), and administration of MMRV combined vaccine is similar to administration of MMR and varicella vaccines on the same day (*18*). No evidence exists that oral rotavirus vaccine (RV) interferes with live vaccines administered by injection or intranasally (e.g., MMR and live-attenuated influenza vaccine [LAIV]). RV can be administered simultaneously or at any interval before or after injectable or intranasal live vaccines (*19*). No data exist about the immunogenicity of oral Ty21a typhoid vaccine when administered concurrently or within 30 days of other live virus vaccines. In the absence of such data, if typhoid vaccination is warranted, administration should not be delayed because of administration of live-attenuated virus vaccines (*20*).

Simultaneously administering pneumococcal polysaccharide vaccine (PPV) and inactivated influenza vaccine elicits a satisfactory antibody response without increasing the incidence or severity of adverse reactions (*21*). Simultaneously administering PPV and inactivated influenza vaccine is recommended for all persons for whom both vaccines are indicated.

Hepatitis B vaccine (HepB) administered with yellow fever vaccine is as safe and immunogenic as when these vaccines are administered separately (*22*). Measles and yellow fever vaccines have been administered safely at the same visit and without reduction of immunogenicity of each of the components (*23,24*).

Depending on vaccines administered in the first year of life, children aged 12–15 months might receive up to nine injections during a single visit (MMR, varicella, Hib, pneumococcal conjugate, diphtheria and tetanus toxoids and acellular pertussis [DTaP], IPV, hepatitis A, HepB, and influenza [seasonal] vaccines). To reduce the number of injections at the 12–15-month visit, the IPV and HepB series can be expedited and completed before the child's first birthday. MMRV can be administered as soon as possible on or after the first birthday and the fourth dose of DTaP administered at age 15 months. The majority of children aged 1 year who have received 2 (polyribosylribitol phosphate-meningococcal outer membrane protein [PRP-OMP]) or 3 (PRP-tetanus [PRP-T], diphtheria CRM197 [CRM, cross-reactive material] protein conjugate [HbOC]) previous doses of Hib vaccine and 3 previous doses of DTaP and pneumococcal conjugate vaccine (PCV) have had protection (*25,26*). The third (PRP-OMP) or fourth (PRP-T, HbOC) dose of the Hib series, and the fourth doses of DTaP and PCV are critical in boosting antibody titer and ensuring continued protection (*26–29*). However, the booster dose of the pneumococcal conjugate series can be deferred until age 15–18 months for children who are likely to return for future visits. The fourth dose of DTaP is recommended at age 15–18 months but can be administered as early as age 12 months under certain circumstances (*27*). For infants at low risk for infection with hepatitis B virus (i.e., the mother tested negative for hepatitis B surface antigen [HBsAg] at the time of delivery), the HepB series can be completed at any time for children aged 6–18 months. With use of certain HepB combination vaccines (i.e., combination Hib-HepB vaccine), the minimum age of administration of the final dose is 12 months because of the minimum age requirement for the last dose of the Hib series (*30*). Recommended spacing of doses should be maintained (Table 1).

Use of combination vaccines can reduce the number of injections required at an office visit. Licensed combination vaccines can be used whenever any components of the combination are indicated and its other components are not contraindicated and if licensed by the Food and Drug Administration (FDA) for that dose in the series. Use of licensed combination vaccines is preferred to separate injection of their equivalent component vaccines to reduce the number of injections and missed opportunities to protect through vaccination (*31*). Only combination vaccines licensed by FDA should be used. Individual vaccines should never be mixed in the same syringe unless they are approved specifically for mixing by FDA. Only one vaccine (DTaP and PRP-T Hib vaccine, marketed as TriHIBit® [manufactured by sanofi pasteur]) is licensed by FDA for mixing in the same syringe. This vaccine should not be used for primary vaccination in infants aged 2, 4, and 6 months, but it can be used as the last dose of the Hib vaccine series on or after age 12 months.

Nonsimultaneous Administration

No evidence exists that inactivated vaccines interfere with the immune response to other inactivated vaccines or to live vaccines. An inactivated vaccine can be administered either simultaneously or at any time before or after a different inactivated vaccine or live vaccine (Table 2).

Data are limited about interference between live vaccines. The immune response to one live-virus vaccine might be impaired if administered within 30 days of another live-virus vaccine (*32,33*). In a study conducted in two U.S. health maintenance organizations, persons who received varicella vaccine <30 days after MMR vaccination had an increased risk for varicella vaccine failure (i.e., varicella disease in a vaccinated person) of 2.5-fold compared with persons who received varicella vaccine before or >30 days after MMR (*34*). In comparison, another study determined that the response to yellow fever vaccine is not affected by monovalent measles vaccine administered 1–27 days earlier (*23*). The effect of nonsimultaneously administering rubella, mumps, varicella, and yellow fever vaccines is unknown.

TABLE 2. Guidelines for spacing of live and inactivated antigens

Antigen combination	Recommended minimum interval between doses
Two or more inactivated*	Can be administered simultaneously or at any interval between doses
Inactivated and live	Can be administered simultaneously or at any interval between doses
Two or more live intranasal or injectable†	4-week minimum interval, if not administered simultaneously

* Certain experts suggest a 1-month interval between tetanus toxoid, reduced diphtheria toxoid, and reduced acellular pertussis vaccine and quadrivalent meningococcal conjugate vaccine if they are not administered simultaneously.

† Live oral vaccines (e.g., Ty21a typhoid vaccine and rotavirus vaccine) can be administered simultaneously or at any interval before or after inactivated or live injectable vaccines.

Source: American Academy of Pediatrics. Pertussis. In: Pickering LK, Backer, CJ, Long SS, McMillan J, eds., Red Book: 2006 Report of the Committee on Infectious Diseases. 27th ed. Elk Grove Village, IL: American Academy of Pediatrics.

To minimize the potential risk for interference, injectable or nasally administered live vaccines not administered on the same day should be administered >4 weeks apart whenever possible (Table 2). If injectable or nasally administered live vaccines are separated by <4 weeks, the vaccine-administered second should not be counted as a valid dose and should be repeated. The repeat dose should be administered >4 weeks after the last invalid dose. Yellow fever vaccine can be administered at any time after single-antigen measles vaccine. Oral vaccines (Ty21a typhoid vaccine and RV) can be administered simultaneously or at any interval before or after other live vaccines (injectable or intranasal) if indicated.

Spacing of Vaccines and Antibody-Containing Products

Live Vaccines

Ty21a typhoid, yellow fever, and LAIV vaccines can be administered at any time before, concurrent with, or after administering any immune globulin, hyperimmune globulin, or intravenous immune globulin (IGIV). Blood (e.g., whole blood, packed red blood cells, and plasma) and other antibody-containing blood products (e.g., immune globulin, hyperimmune globulin, and IGIV) can inhibit the immune response to measles and rubella vaccines for 3 or more months. The effect of blood and immune globulin preparations on the response to mumps and varicella vaccines is unknown, but commercial immune globulin preparations contain antibodies to these viruses. Blood products available in the United States are unlikely to contain a substantial amount of antibody to yellow fever vaccine virus. The length of time that interference with injectable live vaccination (except yellow fever vaccine) can persist after the antibody-containing product is a function of the amount of antigen-specific antibody contained in the product (*35–37*). Therefore, after an antibody-containing product is received, live vaccines (except yellow fever vaccine, oral Ty21a typhoid vaccine, and LAIV) should be delayed until the passive antibody has degraded (Table 3). If a dose of injectable live-virus vaccine (except yellow fever vaccine) is administered after an antibody-containing product but at an interval shorter than recommended in this report, the vaccine dose should be repeated unless serologic testing is feasible and indicates a response to the vac-

TABLE 3. Guidelines for administering antibody-containing products* and vaccines

Simultaneous administration

Combination	Recommended minimum interval between doses
Antibody-containing products and inactivated antigen	Can be administered simultaneously at different sites or at any time interval between doses.
Antibody-containing products and live antigen	Should not be administered simultaneously.† If simultaneous administration of measles-containing vaccine or varicella vaccine is unavoidable, administer at different sites and revaccinate or test for seroconversion after the recommended interval.

Nonsimultaneous administration

Product administered		
First	Second	Recommended minimum interval between doses
Antibody-containing products	Inactivated antigen	Not applicable
Inactivated antigen	Antibody-containing products	Not applicable
Antibody-containing products	Live antigen	Dose-related†,§,¶
Live antigen	Antibody-containing products	2 weeks†

* Blood products containing substantial amounts of immunoglobulin include intramuscular and intravenous immune globulin, specific hyperimmune globulin (e.g., hepatitis B immune globulin, tetanus immune globulin, varicella zoster immune globulin, and rabies immune globulin), whole blood, packed red cells, plasma, and platelet products.

† Yellow fever, oral Ty21a typhoid vaccine, and live-attenuated influenza vaccine are exceptions to these recommendations. These live-attenuated vaccines can be administered at any time before, after, or simultaneously with an antibody-containing product without substantially decreasing the antibody response.

§ Rotavirus vaccine (RV) should be deferred for 6 weeks after receipt of an antibody-containing product if possible. However, if the 6-week deferral would cause the first dose of RV to be scheduled for age ≥13 weeks, a shorter deferral interval should be used to ensure the first dose of RV is administered no later than age 13 weeks.

¶ The duration of interference of antibody-containing products with the immune response to the measles component of measles-containing vaccine, and possibly varicella vaccine, is dose-related.

cine. The repeat dose or serologic testing should be performed after the interval indicated for the antibody-containing product (Table 4).

Although passively acquired antibodies can interfere with the response to rubella vaccine, the low dose of anti-Rho(D) globulin administered to postpartum women has not been demonstrated to reduce the response to the RA27/3 strain rubella vaccine (*38*). Because of the importance of rubella and varicella immunity among childbearing-aged women (*6,39*), the postpartum vaccination of women without evidence of immunity to rubella or varicella with single-antigen rubella, MMR, varicella, or MMRV vaccine should not be delayed because of receipt of anti-Rho(D) globulin or any other blood product during the last trimester of pregnancy or at delivery. These women should be vaccinated immediately after delivery and, if possible, tested 3 or more months later to ensure immunity to rubella and, if appropriate, to measles (*6*).

Interference can occur if administering an antibody-containing product becomes necessary after administering MMRV or its individual components. Usually, vaccine virus replication and stimulation of immunity will occur 1–2 weeks after vaccination. If the interval between administering any of these vaccines and subsequent administration of an antibody-containing product is <14 days, vaccination should be repeated after the recommended interval (Tables 3 and 4), unless serologic testing indicates an antibody response. RV should be deferred for 6 weeks after receipt of an antibody-containing product if possible. However, if the 6-week deferral would cause the first dose of RV to be scheduled for a child aged ≥13 weeks, a shorter deferral interval should be used to ensure the first dose of RV is administered no later than age 13 weeks (*19*).

A humanized mouse monoclonal antibody product (palivizumab) is available for prevention of respiratory syncytial virus infection among infants and young children. This product contains only antibody to respiratory syncytial virus and will not interfere with immune response to currently licensed live or inactivated vaccines.

Inactivated Vaccines

Antibody-containing products interact less with inactivated vaccines, toxoids, recombinant subunit, and polysaccharide vaccines than with live vaccines (*40*). Therefore, administering inactivated vaccines and toxoids either simultaneously with or at any interval before or after receipt of an antibody-containing product should not substantially impair development of a protective antibody response (Table 3). The vaccine or toxoid and antibody preparation should be administered at different sites by using the standard recommended dose. Increasing the vaccine dose volume or number of vaccinations is not indicated or recommended.

TABLE 4. Suggested intervals between administration of antibody-containing products for different indications and measles-containing vaccine and varicella-containing vaccine*

Product/indication	Dose, including mg immunoglobulin G (IgG)/ kg body weight*	Recommended interval before measles or varicella-containing vaccine administration (months)
Respiratory syncytial virus immune globulin (IG) monoclonal antibody (Synagis™)†	15 mg/kg intramuscularly (IM)	None
Tetanus IG	250 units (10 mg IgG/kg) IM	3
Hepatitis A IG		
Contact prophylaxis	0.02 mL/kg (3.3 mg IgG/kg) IM	3
International travel	0.06 mL/kg (10 mg IgG/kg) IM	3
Hepatitis B IG	0.06 mL/kg (10 mg IgG/kg) IM	3
Rabies IG	20 IU/kg (22 mg IgG/kg) IM	4
Measles prophylaxis IG		
Standard (i.e., nonimmunocompromised) contact	0.25 mL/kg (40 mg IgG/kg) IM	5
Immunocompromised contact	0.50 mL/kg (80 mg IgG/kg) IM	6
Blood transfusion		
Red blood cells (RBCs), washed	10 mL/kg negligible IgG/kg intravenously (IV)	None
RBCs, adenine-saline added	10 mL/kg (10 mg IgG/kg) IV	3
Packed RBCs (hematocrit 65%)§	10 mL/kg (60 mg IgG/kg) IV	6
Whole blood (hematocrit 35%–50%)§	10 mL/kg (80–100 mg IgG/kg) IV	6
Plasma/platelet products	10 mL/kg (160 mg IgG/kg) IV	7
Cytomegalovirus intravenous immune globulin (IGIV)	150 mg/kg maximum	6
IGIV		
Replacement therapy for immune deficiencies¶	300–400 mg/kg IV¶	8
Immune thrombocytopenic purpura	400 mg/kg IV	8
Postexposure varicella prophylaxis**	400 mg/kg IV	8
Immune thrombocytopenic purpura	1000 mg/kg IV	10
Kawasaki disease	2 g/kg IV	11

* This table is not intended for determining the correct indications and dosages for using antibody-containing products. Unvaccinated persons might not be fully protected against measles during the entire recommended interval, and additional doses of immune globulin or measles vaccine might be indicated after measles exposure. Concentrations of measles antibody in an immune globulin preparation can vary by manufacturer's lot. Rates of antibody clearance after receipt of an immune globulin preparation also might vary. Recommended intervals are extrapolated from an estimated half-life of 30 days for passively acquired antibody and an observed interference with the immune response to measles vaccine for 5 months after a dose of 80 mg IgG/kg.

† Contains antibody only to respiratory syncytial virus

§ Assumes a serum IgG concentration of 16 mg/mL.

¶ Measles and varicella vaccinations are recommended for children with asymptomatic or mildly symptomatic human immunodeficiency virus (HIV) infection but are contraindicated for persons with severe immunosuppression from HIV or any other immunosuppressive disorder.

** The investigational product VariZIG, similar to licensed VZIG, is a purified human immune globulin preparation made from plasma containing high levels of anti-varicella antibodies (immunoglobulin class G [IgG]). When indicated, health-care providers should make every effort to obtain and administer VariZIG. In situations in which administration of VariZIG does not appear possible within 96 hours of exposure, administration of immune globulin intravenous (IGIV) should be considered as an alternative. IGIV also should be administered within 96 hours of exposure. Although licensed IGIV preparations are known to contain anti-varicella antibody titers, the titer of any specific lot of IGIV that might be available is uncertain because IGIV is not routinely tested for antivaricella antibodies. The recommended IGIV dose for postexposure prophylaxis of varicella is 400 mg/kg, administered once. For pregnant women who cannot receive VariZIG within 96 hours of exposure, clinicians can choose either to administer IGIV or closely monitor the women for signs and symptoms of varicella and institute treatment with acyclovir if illness occurs. (**Source:** CDC. A new product for postexposure prophylaxis available under an investigational new drug application expanded access protocol. MMWR 2006;55:209–10).

Interchangeability of Vaccines from Different Manufacturers

Certain vaccines are available from different manufacturers, and these vaccines usually are not identical in antigen content or amount or method of formulation. Manufacturers use different production processes, and their products might contain different concentrations of antigen per dose or a different stabilizer or preservative.

Available data indicate that infants who receive sequential doses of different Hib conjugate, HepB, and hepatitis A (HepA) vaccines produce a satisfactory antibody response after a complete primary series (*41–44*). All brands of Hib conjugate, HepB,§ and HepA vaccines are interchangeable within

§ The exception is the 2-dose HepB vaccination series for adolescents aged 11–15 years. Only Recombivax HB® (Merck Vaccine Division) should be used in this schedule. Engerix-B® (GlaxoSmithKline) is not approved by FDA for this schedule.

their respective series. If different brands of Hib conjugate vaccine are administered, 3 doses are considered adequate for the primary series among infants. If PRP-OMP is used, the primary series consists of 2 doses. After completing the primary series, any Hib conjugate vaccine can be used for the booster dose at age 12–18 months.

Data are limited about the safety, immunogenicity, and efficacy of using acellular pertussis (e.g., DTaP) vaccines from different manufacturers for successive doses of the pertussis series. Data from one study indicate that, for the first 3 doses of the DTaP series, 1–2 doses of Tripedia® followed by Infanrix® for the remaining doses(s) is comparable to 3 doses of Tripedia with regard to immunogenicity, as measured by antibodies to diphtheria, tetanus, and pertussis toxoid, and filamentous hemagglutinin (*45*). However, in the absence of a clear serologic correlate of protection for pertussis, the relevance of these immunogenicity data for protection against pertussis is unknown. Whenever feasible, the same brand of DTaP vaccine should be used for all doses of the vaccination series. If vaccination providers do not know or have available the type of DTaP vaccine previously administered to a child, any DTaP vaccine should be used to continue or complete the series. For vaccines in general, vaccination should not be deferred because the brand used for previous doses is not available or is unknown (*27,46*).

Lapsed Vaccination Schedule

Vaccination providers should administer vaccines as close to the recommended intervals as possible. However, longer-than-recommended intervals between doses do not reduce final antibody concentrations, although protection might not be attained until the recommended number of doses has been administered. With the exception of oral typhoid vaccine, an interruption in the vaccination schedule does not require restarting the entire series of a vaccine or toxoid or addition of extra doses.

Unknown or Uncertain Vaccination Status

Vaccination providers frequently encounter persons who do not have adequate documentation of vaccinations. Providers should only accept written, dated records as evidence of vaccination. With the exception of influenza vaccine and PPV (*47,48*), self-reported doses of vaccine without written documentation should not be accepted. Although vaccinations should not be postponed if records cannot be found, an attempt to locate missing records should be made by contacting previous health-care providers, reviewing state or local immunization information systems (IIS), and searching for a personally held record. If records cannot be located, these persons should be considered susceptible and should be started on the age-appropriate vaccination schedule. Serologic testing for immunity is an alternative to vaccination for certain antigens (e.g., measles, rubella, hepatitis A, and tetanus).

Contraindications and Precautions

Contraindications and precautions to vaccination dictate circumstances when vaccines should not be administered. The majority of precautions are temporary, and the vaccination can be administered later. A contraindication is a condition in a recipient that increases the risk for a serious adverse reaction. A vaccine should not be administered when a contraindication is present. For example, administering influenza vaccine to a person with an anaphylactic allergy to egg protein could cause serious illness in or death of the recipient.

National standards for pediatric vaccination practices have been established and include true contraindications and precautions to vaccination (Table 5) (*1*). The only contraindication applicable to all vaccines is a history of a severe allergic reaction after a previous dose of vaccine or to a vaccine constituent (unless the recipient has been desensitized). In addition, severely immunocompromised persons should generally not receive live vaccines. Children who experience encephalopathy within 7 days after administration of a previous dose of diphtheria and tetanus toxoids and whole-cell pertussis vaccine (DTP), DTaP, or Tdap not attributable to another identifiable cause should not receive further doses of a vaccine that contains pertussis. Because of the theoretical risk for the fetus, women known to be pregnant should generally not receive live-attenuated virus vaccines.

A precaution is a condition in a recipient that might increase the risk for a serious adverse reaction or that might compromise the ability of the vaccine to produce immunity (e.g., administering measles vaccine to a person with passive immunity to measles from a blood transfusion). A person might experience a more severe reaction to the vaccine than would have otherwise been expected; however, the risk for this happening is less than expected with a contraindication. In general, vaccinations should be deferred when a precaution is present. However, a vaccination might be indicated in the presence of a precaution because the benefit of protection from the vaccine outweighs the risk for an adverse reaction. For example, caution should be exercised in vaccinating a child with DTaP who, within 48 hours of receipt of a previous dose of DTP or DTaP, experienced fever of >104°F (>40.5°C); had persistent, inconsolable crying for 3 or more hours; collapsed or experienced a shock-like state; or had a seizure <3 days after receiving the previous dose of DTP or DTaP. How-

TABLE 5. Contraindications and precautions* to commonly used vaccines

Vaccine	True contraindications and precautions*	Untrue (vaccines can be administered)
General for all routine vaccines, including diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP); pediatric diphtheria-tetanus toxoid (DT); adult tetanus-diphtheria toxoid (Td); tetanus-reduced-diphtheria toxoid and acellular pertussis vaccine (Tdap), inactivated poliovirus vaccine (IPV); measles-mumps-rubella vaccine (MMR); *Haemophilus influenzae* type b vaccine (Hib); hepatitis A vaccine; hepatitis B vaccine; varicella vaccine; Rotavirus vaccine, pneumococcal conjugate vaccine (PCV); inactivated influenza vaccine (TIV); live-attenuated influenza vaccine (LAIV) pneumococcal polysaccharide vaccine (PPV); meningococcal conjugate vaccine (MCV4); meningococcal polysaccharide vaccine (MPSV); human papillomavirus vaccine (HPV); and herpes zoster vaccine (HZ)	**Contraindications** Severe allergic reaction (e.g., anaphylaxis) after a previous vaccine dose or to a vaccine component **Precautions** Moderate or severe acute illness with or without fever	Mild acute illness with or without fever Mild-to-moderate local reaction (i.e., swelling, redness, and soreness); low-grade or moderate fever after previous dose Lack of previous physical examination in well-appearing person Current antimicrobial therapy† Convalescent phase of illness Preterm birth (hepatitis B vaccine is an exception in certain circumstances)§ Recent exposure to an infectious disease History of penicillin allergy, other nonvaccine allergies, relatives with allergies, receiving allergen extract immunotherapy Breast feeding
DTaP	**Contraindications** Severe allergic reaction (e.g., anaphylaxis) after a previous vaccine dose or to a vaccine component Encephalopathy (e.g., coma, decreased level of consciousness; prolonged seizures) not attributable to another identifiable cause within 7 days of administration of previous dose of DTP or DTaP Progressive neurologic disorder, including infantile spasms, uncontrolled epilepsy, progressive encephalopathy: defer DTaP until neurologic status clarified and stabilized **Precautions** Temperature of ≥105°F (≥40.5°C) for ≤48 hours after vaccination with a previous dose of DTP or DTaP Collapse or shock-like state (i.e., hypotonic hyporesponsive episode) ≤48 hours after receiving a previous dose of DTP/DTaP Seizure ≤3 days after receiving a previous dose of DTP/DTaP¶ Persistent, inconsolable crying lasting ≥3 hours within 48 hours after receiving a previous dose of DTP/DTaP Guillain-Barré syndrome (GBS) <6 weeks after previous dose of tetanus toxoid-containing vaccine Moderate or severe acute illness with or without fever	Temperature of ≤104°F (<40.5°C), fussiness, or mild drowsiness after a previous dose of diphtheria toxoid-tetanus toxoid-pertussis vaccine (DTP/DTaP) Family history of seizures¶ Family history of sudden infant death syndrome Family history of an adverse event after DTP or DTaP administration Stable neurologic conditions (e.g., cerebral palsy, well-controlled seizure disorder, developmental delay)
DT, Td	**Contraindications** Severe allergic reaction (e.g., anaphylaxis) after a previous vaccine dose or to a vaccine component **Precautions** GBS <6 weeks after previous dose of tetanus toxoid-containing vaccine Moderate or severe acute illness with or without fever	

TABLE 5. (*Continued*) Contraindications and precautions* to commonly used vaccines

Vaccine	True contraindications and precautions*	Untrue (vaccines can be administered)
Tdap	**Contraindications** Severe allergic reaction (e.g., anaphylaxis) after a previous vaccine dose or to a vaccine component Encephalopathy (e.g., coma, decreased level of consciousness, and prolonged seizures) not attributable to another identifiable cause within 7 days of administration of previous dose of DTP, DTaP or Tdap **Precautions** Moderate or severe acute illness with or without fever GBS ≤6 weeks after a previous dose of tetanus toxoid containing vaccine Progressive or unstable neurological disorder, uncontrolled seizures or progressive encephalopathy until a treatment regimen has been established and the condition has stabilized History of arthus-type hypersensitivity reactions following a previous dose of tetanus toxoid-containing vaccine. Defer vaccination until at least 10 years have elapsed since the last tetanus toxoid-containing vaccine	Temperature of >104° F (>40.5° C) for ≤48 hours after vaccination with a previous dose of DTP or DTaP Collapse or shock-like state (i.e., hypotonic hyporesponsive episode) ≤48 hours after receiving a previous dose of DTP/DTaP Seizure ≤3 days after receiving a previous dose of DTP/DTaP¶ Persistent, inconsolable crying lasting ≥3 hours within 48 hours after receiving a previous dose of DTP/DTaP History of extensive limb swelling after DTP/DTaP/Td that is not an arthus-type reaction Stable neurologic disorder Brachial neuritis Latex allergy that is not anaphylactic Breast feeding Immunosuppression
IPV	**Contraindications** Severe allergic reaction (e.g., anaphylaxis) after a previous vaccine dose or to a vaccine component **Precautions** Pregnancy Moderate or severe acute illness with or without fever	Previous receipt of one or more doses of oral polio vaccine
MMR**	**Contraindications** Severe allergic reaction (e.g., anaphylaxis) after a previous vaccine dose or to a vaccine component Pregnancy Known severe immunodeficiency (e.g., hematologic and solid tumors; receiving chemotherapy; congenital immunodeficiency; long-term immunosuppressive therapy;†† or patients with human immunodeficiency virus [HIV] infection who are severely immunocompromised) **Precautions** Recent (≤11 months) receipt of antibody-containing blood product (specific interval depends on product)¶¶ History of thrombocytopenia or thrombocytopenic purpura Moderate or severe acute illness with or without fever	Positive tuberculin skin test Simultaneous tuberculosis skin testing§§ Breast feeding Pregnancy of recipient's mother or other close or household contact Recipient is childbearing-age female Immunodeficient family member or household contact Asymptomatic or mildly symptomatic HIV infection Allergy to eggs
Hib	**Contraindications** Severe allergic reaction (e.g., anaphylaxis) after a previous vaccine dose or to a vaccine component Aged <6 weeks **Precautions** Moderate or severe acute illness with or without fever	

TABLE 5. (*Continued*) Contraindications and precautions* to commonly used vaccines

Vaccine	True contraindications and precautions*	Untrue (vaccines can be administered)
Hepatitis B	**Contraindication** Severe allergic reaction (e.g., anaphylaxis) after a previous vaccine dose or to a vaccine component **Precautions** Infant weighing <2000 g§ Moderate or severe acute illness with or without fever	Pregnancy Autoimmune disease (e.g., systemic lupus erythematosis or rheumatoid arthritis)
Hepatitis A	**Contraindications** Severe allergic reaction (e.g., anaphylaxis) after a previous vaccine dose or to a vaccine component **Precautions** Pregnancy Moderate or severe acute illness with or without fever	
Varicella	**Contraindications** Severe allergic reaction (e.g., anaphylaxis) after a previous vaccine dose or to a vaccine component Substantial suppression of cellular immunity Pregnancy **Precautions** Recent (≤11 months) receipt of antibody-containing blood product (specific interval depends on product)¶¶ Moderate or severe acute illness with or without fever	Pregnancy of recipient's mother or other close or household contact Immunodeficient family member or household contact*** Asymptomatic or mildly symptomatic HIV infection Humoral immunodeficiency (e.g., agamma-globulinemia)†††
PCV	**Contraindications** Severe allergic reaction (e.g., anaphylaxis) after a previous vaccine dose or to a vaccine component **Precaution** Moderate or severe acute illness with or without fever	
TIV	**Contraindication** Severe allergic reaction (e.g., anaphylaxis) after a previous vaccine dose or to a vaccine component **Precaution** Moderate or severe acute illness with or without fever	Nonsevere (e.g., contact) allergy to latex or thimerosal Concurrent administration of coumadin or aminophylline
LAIV	**Contraindications** Severe allergic reaction (e.g., anaphylaxis) after a previous vaccine dose or to a vaccine component Pregnancy Known severe immunodeficiency (e.g., hematologic and solid tumors; receiving chemotherapy; congenital immunodeficiency; long-term immunosuppressive therapy;†† or patients with human immunodeficiency virus [HIV] infection who are severely immunocompromised) Previous history of GBS Certain chronic medical conditions§§§ **Precaution** Moderate or severe acute illness with or without fever	

TABLE 5. (*Continued*) Contraindications and precautions* to commonly used vaccines

Vaccine	True contraindications and precautions*	Untrue (vaccines can be administered)
PPV	**Contraindication** Severe allergic reaction (e.g., anaphylaxis) after a previous vaccine dose or to a vaccine component **Precaution** Moderate or severe acute illness with or without fever	History of invasive pneumococcal disease or pneumonia
MCV4	**Contraindications** Severe allergic reaction (e.g., anaphylaxis) after a previous vaccine dose or to a vaccine component **Precautions** Moderate or severe acute illness with or without fever History of Guillain-Barré syndrome (if not at high risk for meningococcal disease)	
MPSV	**Contraindications** Severe allergic reaction after a previous dose or to a vaccine component **Precautions** Moderate or severe acute illness with or without fever	
HPV	**Contraindications** Severe allergic reaction after a previous dose or to a vaccine component **Precautions** Moderate or severe acute illness with or without fever Pregnancy	
Rotavirus	**Contraindications** Severe allergic reaction after a previous dose or to a vaccine component **Precautions** Moderate or severe acute illness with or without fever Immunosuppression Receipt of an antibody-containing blood product within 6 weeks¶¶¶ Preexisting gastrointestinal disease Previous history of intussusception	Preterm births Immunosuppression in household contacts Pregnant household contacts

* Events or conditions listed as precautions should be reviewed carefully. Benefits of and risks for administering a specific vaccine to a person under these circumstances should be considered. If the risk from the vaccine is believed to outweigh the benefit, the vaccine should not be administered. If the benefit of vaccination is believed to outweigh the risk, the vaccine should be administered. Whether and when to administer DTaP to children with proven or suspected underlying neurologic disorders should be decided on a case-by-case basis.

† Antibacterial drugs and mefloquine might interfere with Ty21a oral typhoid vaccine, and certain antiviral drugs might interfere with varicella-containing and live-attenuated influenza virus vaccine.

§ Hepatitis B vaccination should be deferred for infants weighing <2000 g if the mother is documented to be hepatitis B surface antigen (HBsAg)-negative at the time of the infant's birth. Vaccination can commence at chronological age 1 month. For infants born to HBsAg-positive women, hepatitis B immunoglobulin and hepatitis B vaccine should be administered at or soon after birth, regardless of weight.

¶ Acetaminophen or other appropriate antipyretic can be administered to infants and children with a history of previous seizures at the time of DTaP vaccination and every 4 hours for 24 hours thereafter to reduce the possibility of postvaccination fever (**Source:** American Academy of Pediatrics. Active immunization. In: Pickering LK, Baker CJ, Long SS, McMillan J. eds. 2006 red book: report of the Committee on Infectious Diseases. 27th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2006).

** MMR and varicella vaccines can be administered on the same day. If not administered on the same day, these vaccines should be separated by at least 28 days.

†† Substantially immunosuppressive steroid dose is considered to be ≥2 weeks of daily receipt of ≥20 mg or ≥2 mg/kg body weight of prednisone or equivalent.

§§ Measles vaccination might suppress tuberculin reactivity temporarily. Measles-containing vaccine can be administered on the same day as tuberculin skin testing. If testing cannot be performed until after the day of MMR vaccination, the test should be postponed for ≥4 weeks after the vaccination. If an urgent need exists to skin test, do so with the understanding that reactivity might be reduced by the vaccine.

¶¶ See text for details

TABLE 5. (*Continued*) Contraindications and precautions* to commonly used vaccines

Vaccine	True contraindications and precautions*	Untrue (vaccines can be administered)

*** If a vaccinee experiences a presumed vaccine-related rash 7–25 days after vaccination, avoid direct contact with immunocompromised persons for the duration of the rash, if possible.

††† Vaccine should be deferred for the appropriate interval if replacement IG products are being administered (Table 4).

§§§ For details, see CDC. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2006;55:No. RR-10.

¶¶¶ Rotavirus vaccine (RV) should be deferred for 6 weeks after receipt of an antibody-containing product if possible. However, if the 6-week deferral would cause the first dose of RV to be scheduled for age ≥13 weeks, a shorter deferral interval should be used to ensure the first dose of RV is administered no later than age 13 weeks.

ever, administering a pertussis-containing vaccine should be considered if the risk for pertussis is increased (e.g., during a pertussis outbreak) (*27*). These precautions do not apply to administration of tetanus-reduced-diphtheria-acellular-pertussis vaccine for adolescents and adults. The presence of a moderate or severe acute illness with or without a fever is a precaution to administration of all vaccines (Table 5).

Clinicians or other health-care providers might inappropriately consider certain conditions or circumstances to be true contraindications or precautions to vaccination. This misconception results in missed opportunities to administer recommended vaccines (*49*). Likewise, clinicians and other health-care providers might fail to understand what constitutes a true contraindication or precaution and might administer a vaccine when it should be withheld. This practice can result in an increased risk for an adverse reaction to the vaccine. Among the most common conditions often inappropriately considered contraindications are diarrhea, minor upper-respiratory tract illnesses (including otitis media) with or without fever, mild-to-moderate local reactions to a previous dose of vaccine, current antimicrobial therapy, and the convalescent phase of an acute illness (Table 5).

The decision to administer or delay vaccination because of a current or recent acute illness depends on severity of symptoms and etiology of the disease. All vaccines can be administered to persons with minor acute illness (e.g., diarrhea or mild upper-respiratory tract infection with or without fever). Studies indicate that failure to vaccinate children with minor illnesses can seriously impede vaccination efforts (*50–52*). Among persons whose compliance with medical care cannot be ensured, use of every opportunity to provide appropriate vaccinations is critical.

The safety and efficacy of vaccinating persons who have mild illnesses have been documented (*53–56*). Vaccination should not be delayed because of the presence of mild respiratory tract illness or other acute illness with or without fever.

Persons with moderate or severe acute illness should be vaccinated as soon as the acute illness has improved, after screening for contraindications. This precaution avoids superimposing adverse effects of the vaccine on the underlying illness or causing diagnostic confusion between manifestations of the underlying illness and possible adverse effects of vaccination.

Routine physical examinations and procedures (e.g., measuring temperatures) are not prerequisites for vaccinating persons who appear to be healthy. Asking the parent or guardian if the child is ill and then postponing vaccination for children with moderate-to-severe illness or proceeding with vaccination if no contraindications exist are appropriate procedures in childhood vaccination programs.

A family history of seizures or other central nervous system disorders is not a contraindication to administration of pertussis or other vaccines. However, delaying pertussis vaccination for infants and children with a history of previous seizures until the child's neurologic status has been assessed is prudent. Pertussis vaccine should not be administered to infants with evolving neurologic conditions until the condition has stabilized (Table 5) (*27*).

Vaccine Administration

Infection Control and Sterile Technique

Persons administering vaccines should follow appropriate precautions to minimize risk for spread of disease. Hands should be cleansed with an alcohol-based waterless antiseptic hand rub or washed with soap and water between each patient contact (*57*). Occupational Safety and Health Administration (OSHA) regulations do not require gloves to be worn when administering vaccinations, unless persons administering vaccinations are likely to come into contact with potentially infectious body fluids or have open lesions on their hands. Needles used for injections must be sterile and disposable to minimize the risk for contamination. A separate needle and syringe should be used for each injection. Changing needles between drawing vaccine from a vial and injecting it into a recipient is not necessary. Different vaccines should never be mixed in the same syringe unless specifically licensed for such use, and no attempt should be made to transfer between syringes.

To prevent inadvertent needle-stick injury or reuse, needles and syringes should be discarded immediately after use in labeled, puncture-proof containers located in the same room where the vaccine is administered. Needles should not be recapped before being placed in the container. Safety needles or needle-free injection devices should be used if available to reduce the risk for injury.

Injection Route and Injection Site

With the exception of Bacillus Calmette-Guerin (BCG) vaccine, injectable vaccines are administered by the intramuscular and subcutaneous route. The method of administration of injectable vaccines is determined, in part, by the presence of adjuvants in some vaccines. The term adjuvant refers to a vaccine component distinct from the antigen that enhances the immune response to the antigen. The majority of vaccines containing an adjuvant (e.g., DTaP, DT, Td, Tdap, PCV, Hib, HepA , HepB, and human papillomavirus [HPV]) should be injected into a muscle because administration subcutaneously or intradermally can cause local irritation, induration, skin discoloration, inflammation, and granuloma formation. Anthrax vaccine, an inactivated vaccine with adjuvant, is an exception to this rule and is recommended to be administered subcutaneously. Routes of administration are recommended by the manufacturer for each immunobiologic (Table 6). Deviation from the recommended route of administration might reduce vaccine efficacy (*58,59*) or increase local adverse reactions (*60–62*).

Intramuscular Injections and Needle Length

Injectable immunobiologics should be administered where local, neural, vascular, or tissue injury is unlikely. Use of longer needles has been associated with less redness or swelling than occurs with shorter needles because of injection into deeper muscle mass (*60*). Appropriate needle length depends on age and body mass.

TABLE 6: Dose and route of administration for selected vaccines

Vaccines	Dose	Route
Diphtheria, tetanus, pertussis (DTaP, DT, Td, Tdap)	0.5 mL	Intramuscular (IM)
Diphtheria, tetanus, acellular pertussis, inactivated polio, hepatitis B vaccine (DTaP-IPV-HepB)	0.5 mL	IM
Diphtheria, tetanus, acellular pertussis, *haemophilus influenza* type b vaccine (DTaP-Hib)	0.5 mL	IM
Haemophilus influenzae type b (Hib)	0.5 mL	IM
Haemophilus influenzae type b – Hepatitis B (Hib-HepB)	0.5 mL	IM
Hepatitis A (HepA)	≤18 yrs: 0.5 mL ≥19 yrs: 1.0 mL	IM
HepB	≤19 yrs: 0.5 mL* ≥20 yrs: 1.0 mL	IM
HepA/HepB	≥18 yrs: 1.0 mL	IM
Influenza, live attenuated	0.5 mL	Intranasal spray
Influenza, trivalent inactivated	6–35 mos: 0.25 mL ≥3 yrs: 0.5 mL	IM
Measles, mumps, rubella	0.5 mL	Subcutaneous (SC)
Measles, mumps, rubella, varicella	0.5 mL	SC
Meningococcal conjugate	0.5 mL	IM
Meningococcal polysaccharide	0.5 mL	SC
Pneumococcal conjugate	0.5 mL	IM
Pneumococcal polysaccharide	0.5 mL	IM or SC
Human papillomavirus	0.5 mL	IM
Polio, inactivated	0.5 mL	IM or SC
Rotavirus	2.0 mL	Oral
Varicella	0.5 mL	SC
Zoster	0.7 mL	SC

* Persons aged 11–15 years can be administered Recombivax HB® (Merck) 1.0 mL (adult formulation) on a 2-dose schedule.
Adapted from: Immunization Action Coalition (http://www.immunize.org).

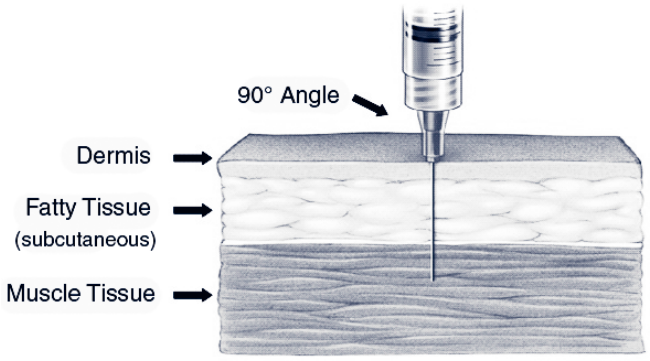
For all intramuscular injections, the needle should be long enough to reach the muscle mass and prevent vaccine from seeping into subcutaneous tissue, but not so long as to involve underlying nerves, blood vessels, or bone (*59,63–65*). Vaccinators should be familiar with the anatomy of the area into which they are injecting vaccine. Intramuscular injections are administered at a 90-degree angle to the skin, preferably into the anterolateral aspect of the thigh or the deltoid muscle of the upper arm, depending on the age of the patient (Table 7).

Decision on needle size and site of injection must be made for each person on the basis of the size of the muscle, the thickness of adipose tissue at the injection site, the volume of the material to be administered, injection technique, and the depth below the muscle surface into which the material is to be injected (Figure 1). Aspiration before injection of vaccines or toxoids (i.e., pulling back on the syringe plunger after needle insertion, before injection) is not required because no large blood vessels exists at the recommended injection sites.

Infants (Aged <12 Months)

For the majority of infants, the anterolateral aspect of the thigh is the recommended site for injection because it provides a large muscle mass (Figure 2). The muscles of the buttock have not been used for administration of vaccines in infants and children because of concern about potential injury to the sciatic nerve, which is well documented after injection of antimicrobial agents into the buttock. If the gluteal muscle must be used, care should be taken to define the ana-

FIGURE 1. Intramuscular needle insertion



Adapted from California Immunization Branch

FIGURE 2. Intramuscular/subcutaneous site of administration: anterolateral thigh



Adapted from Minnesota Department of Health

TABLE 7. Needle length and injection site of intramuscular injections

	Birth–18 years	
Age	**Needle length**	**Injection site**
Newborn*	5/8" (16mm)†	Anterolateral thigh
Infant 1–12 months	1" (25mm)	Anterolateral thigh
Toddler 1 – 2 years	1"–1 1/4" (25–32 mm) 5/8"†–1" (16–25 mm)	Anterolateral thigh§ Deltoid muscle of the arm
Child/adolescent 3–18 years	5/8"†–1" (16–25 mm) 1"–1 1/4" (25–32 mm)	Deltoid muscle of the arm§ Anterolateral thigh
	Aged ≥19 Years	
Sex/weight	**Needle length**	**Injection site**
Male and female <60 kg (130 lbs)	1" (25mm)¶	Deltoid muscle of the arm
Female 60–90 kg (130–200 lbs)	1"–1½" (25–38 mm)	
Male 60–118 kg (130–260 lbs)		
Female >90 kg (200 lbs)	1½" (38 mm)	
Male >118 kg (260 lbs)		

* Newborn = first 28 days of life.
† If skin stretched tight, subcutaneous tissues not bunched.
§ Preferred site.
¶ Certain experts recommend a 5/8" (16 mm) needle for males and females who weigh <60 kg (130 lbs).
Adapted from: Poland GA, Borrud A, Jacobsen RM, et al. Determination of deltoid fat pad thickness: implications for needle length in adult immunization. JAMA 1997;277: 1709–11.

Please note: *Errata have been published for this article. To view the errata, please click here and here.*

tomic landmarks.[¶] Injection technique is the most important parameter to ensure efficient intramuscular vaccine delivery. If the subcutaneous and muscle tissue are bunched to minimize the chance of striking bone (*63*), a 1-inch needle is required to ensure intramuscular administration in infants. For the majority of infants, a 1-inch, 22–25-gauge needle is sufficient to penetrate muscle in an infant's thigh. For newborn (first 28 days of life) and premature infants, a 5/8 inch long needle usually is adequate if the skin is stretched flat between thumb and forefinger and the needle inserted at a 90-degree angle to the skin (*65*).

Toddlers and Older Children (Aged 12 Months–10 Years)

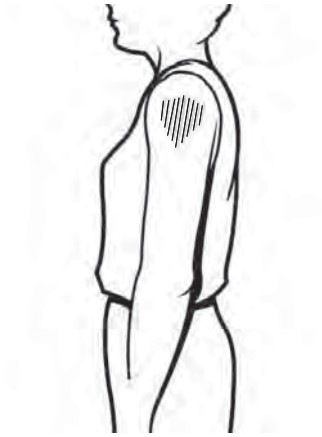
The deltoid muscle should be used if the muscle mass is adequate. The needle size for deltoid site injections can range from 22–25 gauge and from 5/8 to 1 inch on the basis of the size of the muscle and the thickness of adipose tissue at the injection site (Figure 3). A 5/8-inch needle is adequate only for the deltoid muscle and only if the skin is stretched flat between thumb and forefinger and the needle inserted at a 90-degree angle to the skin. For toddlers, the anterolateral thigh can be used, but the needle should be at least 1 inch in length.

Adolescents and Adults (Aged >11 Years)

For adults and adolescents, the deltoid muscle is recommended for routine intramuscular vaccinations. The anterolateral thigh also can be used. For men and women weighing <130 lbs (<60 kg) a 5/8–1-inch needle is sufficient to ensure intramuscular injection. For women weighing 130–200 lbs (60–90 kg) and men 130–260 lbs (60–118kg), a 1–1½-inch needle is needed. For women weighing >200 lbs (>90 kg) or men weighing >260 lbs (>118 kg), a 1½-inch needle is required (Table 7) (*64*).

[¶]If the gluteal muscle is chosen, injection should be administered lateral and superior to a line between the posterior superior iliac spine and the greater trochanter or in the ventrogluteal site, the center of a triangle bounded by the anterior superior iliac spine, the tubercle of the iliac crest, and the upper border of the greater trochanter.

FIGURE 3. Intramuscular site of administration: deltoid



Adapted from Minnesota Department of Health

Subcutaneous Injections

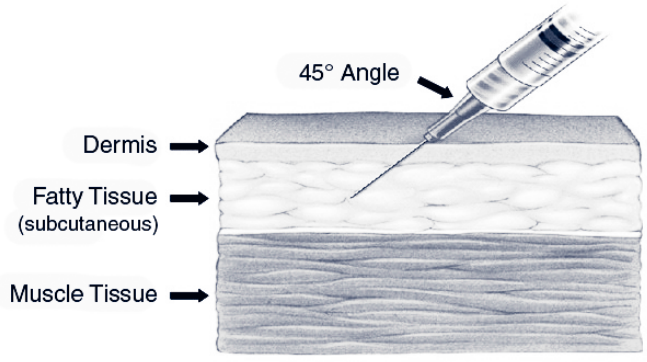
Subcutaneous injections are administered at a 45-degree angle usually into the thigh for infants aged <12 months and in the upper-outer triceps area of persons aged ≥12 months. Subcutaneous injections can be administered into the upper-outer triceps area of an infant, if necessary. A 5/8-inch, 23–25-gauge needle should be inserted into the subcutaneous tissue (Figures 4 and 5).

FIGURE 4. Subcutaneous site of administration: triceps



Adapted from Minnesota Department of Health

FIGURE 5. Subcutaneous needle insertion



Adapted from California Immunization Branch

Multiple Vaccinations

If multiple vaccines are administered at a single visit, administration of each preparation at a different anatomic site is desirable. For infants and younger children, if more than two vaccines must be injected in a single limb, the thigh is the preferred site because of the greater muscle mass; the injections should be sufficiently separated (i.e., 1 inch or more if possible) so that any local reactions can be differentiated (*60,66*). For older children and adults, the deltoid muscle can be used for more than one intramuscular injection. If a vaccine and an immune globulin preparation are administered simultaneously (e.g., Td/Tdap and tetanus immune globulin [TIG], HepB and hepatitis B immunoglobulin [HBIG]), separate anatomic sites should be used for each injection. The location of each injection should be documented in the patients' medical record.

Jet Injection

Jet injectors (JIs) are needle-free devices that drive liquid medication through a nozzle orifice, creating a narrow stream under high pressure that penetrates skin to deliver a drug or vaccine into intradermal, subcutaneous, or intramuscular tissues (*67,68*). JIs have the potential to reduce the frequency of needle-stick injuries to health-care workers (*69*) and to overcome the improper reuse and other drawbacks of needles and syringes in economically developing countries (*70–72*). JIs have been safe and effective for administering different live and inactivated vaccines for viral and bacterial diseases (*72*). The immune responses generated are equivalent to, and occasionally greater than, immune responses induced by needle injection. However, local reactions or injury (e.g., redness, induration, pain, blood, and ecchymosis at the injection site) can be more frequent when vaccines are delivered by JIs compared with needle injection (*68,72*).

In the 1990s, a new generation of JIs was introduced with disposable cartridges serving as dose chambers and nozzle (*72*). With the provision of a new sterile cartridge for each patient and correct use, these devices avoid the safety concerns for multiple-use–nozzle devices (*72–76*). These devices should be used in accordance with their labeling for intradermal, subcutaneous, or intramuscular administration.

Methods for Alleviating Discomfort and Pain Associated with Vaccination

Comfort measures, such as distraction (e.g., playing music or pretending to blow away the pain), ingestion of sweet liquids, breast feeding, cooling of the injection site, and topical or oral analgesia, can help infants or children cope with the discomfort associated with vaccination (*77,78*). Pretreatment (30–60 minutes before injection) with 5% topical lidocaine-prilocaine emulsion can decrease the pain of vaccination by causing superficial anesthesia (*79,80*). Evidence indicates that this cream does not interfere with the immune response to MMR (*81*). Topical lidocaine-prilocaine emulsion should not be used on infants aged <12 months who are receiving treatment with methemoglobin-inducing agents because of the possible development of methemoglobinemia (*82*).

Acetaminophen has been used among children to reduce the discomfort and fever associated with DTP vaccination (*83*). However, acetaminophen can cause formation of methemoglobin and might interact with lidocaine-prilocaine cream if used concurrently (*82*). Use of a topical refrigerant (vapocoolant) spray immediately before vaccination can reduce the short-term pain associated with injections and can be as effective as lidocaine-prilocaine cream (*84*).

Nonstandard Vaccination Practices

Recommendations for route, site, and dosage of immunobiologics are derived from data from clinical trials, from practical experience, and from theoretical considerations. ACIP discourages variations from the recommended route, site, volume, or number of doses of any vaccine.

Variation from the recommended route and site can result in inadequate protection. In adults but not in infants (*85*), the immunogenicity of HepB is substantially lower when the gluteal rather than the deltoid site is used for administration (*58*). HepB administered intradermally can result in a lower seroconversion rate and final titer of hepatitis B surface antibody than when administered by the deltoid intramuscular route (*86,87*). HepB administered by any route other than intramuscularly, or in adults at any site other than the deltoid or anterolateral thigh, should not be counted as valid and should be repeated. Similarly, doses of rabies vaccine administered in the gluteal site should not be counted as valid doses and should be repeated (*88*). Meningococcal conjugate vaccine (MCV4) should be administered intramuscularly; however, revaccination is not necessary when administered subcutaneously (*89*). Inactivated influenza vaccine is immunogenic when administered in a lower than standard dose by the intradermal (ID) route to healthy adult volunteers (*90*). However, the immunogenicity for persons aged ≥60 years is inadequate, and variance from the recommended route and dose is not recommended.

Live-attenuated injectable vaccines (e.g., MMR, varicella, and yellow fever) and certain inactivated vaccines (e.g., meningococcal polysaccharide and anthrax) are recommended by the manufacturers to be administered by subcutaneous injec-

tion. PPV and IPV are recommended by the manufacturer to be administered by the subcutaneous or intramuscular route. Response to vaccines recommended by the subcutaneous route probably will not be affected if the vaccines are administered by the intramuscular rather than subcutaneous route. Repeating doses of vaccine administered by the intramuscular route rather than by the subcutaneous route is not necessary.

Administering volumes smaller than that recommended (e.g., split doses) can result in inadequate protection. Using larger than recommended dosages can be hazardous because of excessive local or systemic concentrations of antigens or other vaccine constituents. Using reduced doses administered at multiple immunization visits that equal a full dose or using smaller divided doses are not endorsed or recommended. Any vaccination using less than the standard dose should not be counted, and the person should be revaccinated according to age, unless serologic testing indicates that an adequate response has been achieved.

Preventing Adverse Reactions

Vaccines are intended to produce active immunity to specific antigens. An adverse reaction is an untoward effect that occurs after a vaccination that is extraneous to the vaccine's primary purpose of producing immunity. Vaccine adverse reactions are classified by three general categories: local, systemic, and allergic (*91*). Local reactions are usually the least severe and most frequent. Systemic reactions (e.g., fever) occur less frequently than local reactions. Serious allergic reactions (e.g., anaphylaxis) are the most severe and least frequent. Severe adverse reactions are rare.

Persons who administer vaccines should screen their patients for contraindications and precautions to the vaccine before each dose of vaccine is administered (Table 5). Screening can be facilitated by consistent use of screening questionnaires, which are available from certain state vaccination programs and other sources (e.g., the Immunization Action Coalition at http://www.immunize.org).

Syncope (vasovagal or vasodepressor reaction) can occur after vaccination, most commonly among adolescents and young adults. During 1990–2004, a total of 3,168 reports to Vaccine Adverse Event Reporting System (VAERS) were coded as syncope; 35% of these episodes were reported among persons aged 10–18 years (CDC, unpublished data, 2005). Approximately 14% of reported syncopal episodes resulted in hospitalization because of injury or medical evaluation. Serious injury, including skull fracture and cerebral hemorrhage, has resulted from syncopal episodes after vaccination (*92*). A review of syncope after vaccination indicated that 63% of syncopal episodes occurred ≤5 minutes after vaccination, and 89% occurred within 15 minutes after vaccination (*93*). Although syncopal episodes are uncommon and severe allergic reactions are rare, vaccine providers should strongly consider observing patients for 15 minutes after they are vaccinated (*94*). If syncope develops, patients should be observed until the symptoms resolve.

Managing Acute Vaccine Reactions

Although rare after vaccination, the immediate onset and life-threatening nature of an anaphylactic reaction require that all personnel and facilities providing vaccinations have procedures in place for managing a reaction. All vaccine providers should be familiar with the office emergency plan and be certified in cardiopulmonary resuscitation. Epinephrine and equipment for maintaining an airway should be available for immediate use.

Anaphylaxis usually begins within minutes of vaccine administration (*95,96*). Rapidly recognizing and initiating treatment are required to prevent possible progression to cardiovascular collapse. If flushing, facial edema, urticaria, itching, swelling of the mouth or throat, wheezing, difficulty breathing, or other signs of anaphylaxis occur, the patient should be placed in a recumbent position with the legs elevated. Treatment options for management of anaphylaxis using pharmaceuticals have been recommended (Table 8) (*94,97*). Maintenance of an airway and oxygen administration might be necessary. Arrangements should be made for immediate transfer to an emergency facility for further evaluation and treatment.

Occupational Safety Regulations

Bloodborne diseases (e.g., hepatitis B, hepatitis C, and human immunodeficiency virus [HIV]) are occupational hazards for physicians and other health-care providers. To reduce the incidence of needle-stick injury and the consequent risk for bloodborne diseases acquired from patients, the Needlestick Safety and Prevention Act was enacted in November 2000. The Act directed OSHA to strengthen its existing bloodborne pathogen standards. Those standards were revised and became effective in April 2001 (*69*). These federal regulations require that safer injection devices (e.g., needle-shielding syringes or needle-free injectors) be used for injectable vaccination in all clinical settings. The rules also require that records be kept documenting injuries caused by medical sharps and that nonmanagerial employees be involved in the evaluation and selection of safer devices to be procured.

Needle-shielding or needle-free devices that might satisfy the occupational safety regulations for administering inject-

TABLE 8. Treatment of anaphylaxis with intramuscular or oral pharmaceuticals

Drug	Dosage
Child	
Primary regimen	
Epinephrine 1:1000 (aqueous) (1 mg/mL)*	0.01 mg/kg up to 0.5 mg (administer 0.01 mL/kg/dose up to 0.5 mL) intramuscularly (IM) repeated every 10–20 minutes up to 3 doses
Secondary regimen	
Diphenhydramine	1–2 mg/kg oral, IM, or intraveneously (IV), every 4–6 hours (maximum single dose: 100 mg)
Hydroxyzine	0.5–1 mg/kg oral, IM, every 4–6 hours (maximum single dose: 100 mg)
Prednisone	1.5–2 mg/kg oral (maximum single dose: 60 mg); use corticosteroids as long as needed
Adult	
Primary regimen	
Epinephrine 1:1000 (aqueous)*	0.01 mg/kg up to 0.5 mg (give 0.01 mL/kg/dose up to 0.5 mL) IM repeated every 10–20 minutes up to 3 doses
Secondary regimen	
Diphenhydramine	1–2 mg/kg up to 100 mg IM or oral, every 4–6 hours

* If agent causing anaphylactic reaction was administered by injection, epinephrine can be injected into the same site to slow absorption.
Adapted from American Academy of Pediatrics. Passive immunization. In: Pickering LK, Baker CJ, Long SS, McMillan J. Red Book: 2006 Report of the Committee on Infectious Diseases. 27th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2006, Immunization Action Coalition. Medical Management of Anaphylaxis in Adult Patients. Available at http://www.immunize.org/catg.d/p3082.pdf, and Mosby's Drug Consult 2005.

able vaccines are available in the United States (*72,98,99*).** Additional information about implementation and enforcement of these regulations is available from OSHA (http://www.osha.gov/pls/oshaweb).

Storage and Handling of Immunobiologics

Failure to adhere to recommended specifications for storage and handling of immunobiologics can reduce their potency, resulting in an inadequate immune response in the recipient. Recommendations in the product package inserts, including methods for reconstitution of the vaccine, should be followed carefully. Vaccine quality is the shared responsibility of all handlers of vaccines from the time a vaccine is manufactured until administration. All vaccines should be inspected upon delivery and monitored during storage to ensure that the cold chain has been maintained. Vaccines should continue to be stored at recommended temperatures immediately upon receipt until use.

Storage Temperature

The majority of recommended vaccines require storage temperatures of 35°F–46°F (2°C–8°C), and they must not be exposed to freezing temperatures (*100*). Certain vaccines are sensitive to freezing temperatures because they contain an aluminum adjuvant (e.g., anthrax, DTaP, DT, Td, Tdap, Hib [PRP-OMP], HepA, HepB, PCV, rabies, and HPV) that precipitates when exposed to temperatures of ≤32°F (≤0°C) (*100,101*). Other vaccines (e.g., MMR, varicella, MMRV, LAIV, and yellow fever) lose potency when exposed to increased temperature because they contain live viruses (Table 9).

Vaccine storage units must be carefully selected, used properly, and consistently monitored to ensure that recommended temperatures are maintained. Refrigerators without freezers and stand-alone freezers (either manual defrost or automatic defrost) usually perform best at maintaining the precise temperatures required for vaccine storage, and such single-purpose units sold for home use are less expensive alternatives to medical specialty equipment (*100*). A combination refrigerator/freezer unit sold for home use is acceptable for storage of limited quantities of vaccines if the refrigerator and freezer compartments each have a separate external door. In these units, a freezer thermostat usually controls the freezer temperature and a refrigerator thermostat controls the volume of freezer temperature air entering the refrigerator, possibly resulting in different temperature zones within the refrigerator. In such units, vaccines should not be stored on the top shelf near the cold air outlet from the freezer to the refrigerator (usually located at the top of the refrigerator compartment). Any refrigerator or freezer used for vaccine storage must maintain the required temperature range year-round, be large enough to hold the year's largest inventory, and be dedicated to storage of biologics. Before use of the refrigerator for vaccine storage, the temperature should be measured in various

**Internet sites with device listings are identified for information purposes only. CDC, the U.S. Public Health Service, and the Department of Health and Human Services do not endorse any specific device or imply that the devices listed would all satisfy the needle-stick prevention regulations.

Please note: *Errata have been published for this article. To view the errata, please click here and here.*

TABLE 9. Vaccine storage temperature recommendations

Vaccines	Vaccine storage temperature	Diluent storage temperature	Instructions
Diphtheria-tetanus, or pertussis-containing vaccines	35°F–46°F (2°C–8°C) Do not freeze	No diluent*	Aluminum adjuvant – irreversible loss of potency with exposure to freezing temperature
Haemophilus influenzae type b conjugate vaccines (Hib)	35°F–46°F (2°C–8°C) Do not freeze	35°F–46°F (2°C–8°C) Do not freeze	Several vaccine types with different thermo-stability profiles†
Hepatitis A and hepatitis B vaccines	35°F–46°F (2°C–8°C) Do not freeze	No diluent	Aluminum adjuvant – irreversible loss of potency with exposure to freezing temperature
Inactivated polio vaccine	35°F–46°F (2°C–8°C) Do not freeze	No diluent	Data on thermostability properties of this vaccine are lacking
Meningococcal conjugate vaccine	35°F–46°F (2°C–8°C) Do not freeze	No diluent	Data on thermostability properties of this vaccine are lacking. Do not expose to light
Meningococcal polysaccharide vaccine	35°F–46°F (2°C–8°C) Do not freeze	Data are lacking on ideal pre-reconstitution storage requirements. After reconstitution, vaccine should be stored at 35°F–46°F (2°C–8°C).Do not freeze	Freeze dried (lyophilized) vaccine. Data on the effect of freezing temperatures on potency are lacking
Pneumococcal conjugate vaccine	35°F–46°F (2°C–8°C) Do not freeze	No diluent	Aluminum adjuvant – irreversible loss of potency with exposure to freezing temperatures
Pneumococcal polysaccharide vaccine	35°F–46°F (2°C–8°C) Do not freeze	No diluent	Data on thermostability properties of this vaccine are lacking
Measles, mumps, and rubella vaccine in the lyophilized (freeze-dried) state§	35°F–46°F (2°C–8°C) Lyophilized (freeze dried) vaccine can be stored at freezer temperature	35°F–77°F (2°C–25°C) Can be refrigerated or stored at room temperature	Protect from light or temperatures above the recommended range
Measles, mumps, rubella, and varicella vaccine	≤5°F (≤15°C)	35°F–77°F (2°C–25°C) Can be refrigerated or stored at room temperature	Protect from light
Trivalent inactivated influenza vaccine	35°F–46°F (2°C–8°C) Do not freeze	No diluent	Data on the thermostability properties of this vaccine are lacking
Live-attenuated influenza vaccine	≤5°F (≤15°C)	No diluent	Do not expose to temperatures above the recommended range
Varicella vaccine	≤5°F (≤15°C)	35°F–77°F (2°C–25°C) Can be refrigerated or stored at room temperature	Do not expose to light or temperatures above the recommended range
Herpes zoster vaccine	≤5°F (≤15°C)	35°F–77°F (2°C–25°C) Can be refrigerated or stored at room temperature	Protect from light
Rotavirus	35°F–46°F (2°C–8°C) Do not freeze	No diluent	Protect from light
Human papillomavirus vaccine	35°F–46°F (2°C–8°C) Do not freeze	No diluent	Protect from light

* DTaP–Tripedia® is sometimes used as a diluent for ActHib®
† ActHIB® (Aventis Pasteur, Lyon, France) in the lyophilized state is not expected to be affected detrimentally by freezing temperatures, although no data are available.
§ MMR in the lyophilized state is not affected detrimentally by freezing temperatures.
Adapted from Atkinson WL, Pickering LK, Watson JC, Peter G. General Immunization Practices. In: Plotkin SA, Orenstein WA, eds. Vaccine. 4th ed. Philadelphia: Elsevier; 2004. p. 1357-86 and CDC. Guidelines for maintaining and managing the vaccine cold chain. MMWR 2003;52:1023–5.

locations within the refrigerator compartment to document that a stable temperature can be maintained (Table 9) within the compartment (*102*). The refrigerator temperature should be set at the midpoint of the recommended range (i.e., 40°F [5°C]) (*103,104*). Frequent opening and closing of doors can cause fluctuations of storage temperature; food, beverages, and clinical specimens should not be stored in vaccine storage units.

Temperature Monitoring

Temperature monitoring is a critical component of cold chain management. One person in the office should be assigned primary responsibility for maintaining temperature logs (Figure 6), with a second person assigned as backup. Temperatures for both the refrigerator and freezer should be documented twice a day and recorded. The backup person should review the log each week. Temperature logs should be maintained for 3 years unless state or local statutes mandate a longer time period. An automated monitoring system that alerts staff when a temperature deviation occurs is optimal. However, even if an automated monitoring system is used, temperatures should still be manually checked and recorded twice a day.

Thermometers should be placed in a central location in each compartment near the vaccine. Different types of thermometers can be used, including standard fluid-filled, minimum-maximum, and continuous chart recorder thermometers (Table 10). Standard fluid-filled thermometers are the simplest and least expensive products, but some models might

FIGURE 6. Sample temperature log

Temperature Log for Vaccines (Fahrenheit) **Month/Year:**_____ **Days 1–15**

***Instructions:** Place an "X" in the box that corresponds with the temperature. The hatched zones represent unacceptable temperature ranges. If the temperature recorded is in the hatched zone: 1. **Store the vaccine** under proper conditions as quickly as possible, 2. **Call the vaccine manufacturer(s)** to determine whether the potency of the vaccine(s) has been affected, 3. **Call the immunization program at your local health department** for further assistance: (_____) _____, and 4. **Document the action taken** on the reverse side of this log.

Day of Month	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Exact Time															
°F Temp	am pm	am pm	am pm	am pm	am pm	am pm	am pm	am pm	am pm	am pm	am pm	am pm	am pm	am pm	am pm
≥49°															
48°		Take immediate action if temperature is in shaded section*													
47°															
46°															
45°															
44°															
43°															
42°															
41°															
40°															
39°															
38°															
37°															
36°															
35°															
34°															
33°															
32°															
31°		Take immediate action if temperature is in shaded section*													
30°															
29°															
≤28°															
≥8°															
7°															
6°															
5°															
4°															
≤3°															
Room temp															
Staff Initials															

Refrigerator temperature

Freezer temp

Adapted by the Immunization Action Coalition courtesy of the Michigan Department of Community Health

www.immunize.org/catg.d/p3039.pdf • Item #P3039 (11/05)

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TABLE 10. Comparison of thermometers used to monitor vaccine temperatures

Thermometer type	Advantages	Disadvantages
Standard fluid-filled	• Inexpensive and simple to use • Thermometers encased in biosafe liquids can reflect vaccine temperatures more accurately than those directly exposed to the air	• Accurate within a range of (+/-1° C) • No information about duration of out-of-temperature exposure • No information on minimum/maximum temperatures • Cannot be recalibrated at routine intervals • Inexpensive models might perform poorly
Minimum-maximum	• Inexpensive • Monitors temperature range	• Accurate within a range of (+/-1° C.) • No information about the duration of out-of-range temperature • Cannot be recalibrated at routine intervals
Continuous chart recorder	• Most accurate • Continuous 24-hour readings of temperature range and duration • Can be recalibrated at regular intervals	• Most expensive • Requires most training and maintenance

Adapted from CDC. Guidelines for maintaining and managing the vaccine cold chain. MMWR 2003;52:1023–25; and Langley A, Grant S, eds. Proceedings of the National Vaccine Storage Workshop; June 28-30, 2003; Brisbane, Australia. Maroochydore Queensland Health; 2004.

perform poorly. Product temperature thermometers (i.e., those encased in biosafe liquids) generally reflect refrigerator temperature more accurately. Minimum-maximum thermometers monitor the temperature range. Continuous chart recorder thermometers monitor temperature range and duration and can be recalibrated at specified intervals. All thermometers used for monitoring vaccine storage temperatures should be calibrated and certified by an appropriate agency (e.g., National Institute of Standards and Technology or the American Society for Testing and Materials). Because all thermometers are calibrated as part of the manufacturing process, this recommendation refers to a second calibration process that occurs after manufacturing but before marketing and is documented with a certificate that comes with the product.

Response to Out-of-Temperature-Range Storage

An out-of-range temperature reading should prompt immediate action. A plan should be developed to transfer vaccine to a predesignated alternative emergency storage site if a temperature problem cannot be resolved immediately (i.e., unit unplugged or door left open). Vaccine should be marked "do not use" and moved to the alternate site. After the vaccine has been moved, determine if the vaccine is still useable by contacting the manufacturer or state/local health department. Changes to vaccine exposed to temperatures outside of the recommended range and that affects its immunogenicity usually are not apparent visually.

Expiration Dates and Windows

All vaccines have an expiration date determined by the manufacturer that must be observed. When vaccines are removed from storage, physicians and health-care providers should note whether an expiration window exists for vaccine stored at room temperature or at an intermediate temperature. For example, live-attenuated influenza vaccine that is stored frozen must be discarded after 60 hours at refrigerator temperature. An expiration window also applies to vaccines that have been reconstituted. For example, after reconstitution, MMR vaccine must be administered within 8 hours and must be kept at refrigerator temperature during this time. Doses of expired vaccines that are administered inadvertently generally should not be counted as valid and should be repeated. Additional information about expiration dates is available at http://www.cdc.gov/nip.

Multidose Vials

Certain vaccines (i.e., DT, Td, Typhoid Vi, meningococcal polysaccharide vaccine [MPSV], TIV, JE, MMR, IPV, and yellow fever) might be distributed in multidose vials. For multidose vials that do not require reconstitution, after entering the vial, the remaining doses in a multidose vial can be administered until the expiration date printed on the vial or vaccine packaging if the vial has been stored correctly and the vaccine is not visibly contaminated, unless otherwise specified by the manufacturer. Multidose vials that require reconstitution must be used within an interval specified by the manufacturer. After reconstitution, the new expiration date should be written on the vial.

Prefilling Syringes

ACIP discourages the routine practice of prefilling syringes because of the potential for administration errors. The majority of vaccines have a similar appearance after being drawn into a syringe. Vaccine doses should not be drawn into a syringe until immediately before administration. When the syringes are filled, the type of vaccine, lot number, and date of filling must be labeled on each syringe, and the doses should be administered as soon as possible after filling. In certain circumstances in which a single vaccine type is being used (e.g., in advance of a community influenza vaccination campaign), filling a small number of syringes can be considered. Unused syringes filled by the end user (i.e., not filled by the manufacturer) should be discarded at the end of the vaccination session. In addition to administration errors, prefilling of syringes is a concern because FDA does not license administration syringes for vaccine storage. When in doubt about the appropriate handling of a vaccine, vaccination providers should contact the manufacturer.

As a general rule, vaccines that have been mishandled or stored at inappropriate temperatures should not be administered. Guidance for specific situations is available from the state health department or CDC. For certain vaccines (i.e., MMR, MMRV, or varicella vaccine), a serologic test can be performed and, if evidence of immunity can be documented for all antigens, revaccination is not necessary.

Altered Immunocompetence

General Principles

Altered immunocompetence is a term often used synonymously with immunosuppression and immunocompromise that includes conditions commonly classified as primary immunodeficiency and secondary immunodeficiency.

Primary immunodeficiencies generally are inherited and include conditions defined by an absence or quantitative deficiency of cellular and/or humoral components that provide immunity. Examples include congenital immunodeficiency diseases (e.g., X-linked agammaglobulinemia), severe combined immunodeficiency disease, and chronic granulomatous disease. Secondary immunodeficiency generally is acquired and is defined by loss or qualitative deficiency in cellular and humoral immune components that occurs as a result of a disease process or its therapy. Examples of secondary immune deficiency include HIV infection, hematopoetic malignancies, treatment with radiation, and treatment with immunosuppressive drugs, including alkylating agents and antimetabolites. The degree to which immunosuppressive drugs cause clinically significant immunodeficiency generally is dose-related and varies by drug. Primary and secondary immunodeficiencies might display a combination of deficits in both cellular and humoral immunity. In this report, the general term altered immunocompetence also will be used to include conditions such as asplenia and chronic renal disease and treatments with therapeutic monoclonal antibodies (specifically the tumor-necrosis-factor alpha inhibitors) (*105–110*) and prolonged high-dose corticosteroids.

Determination of altered immunocompetence is important to the vaccine provider because the incidence or severity of certain vaccine-preventable diseases is higher in persons with altered immunocompetence; therefore, certain vaccines (e.g., inactivated influenza and pneumococcal vaccines) are recommended specifically for persons with these diseases (*47,111–113*). Vaccines might be less effective during the period of altered immunocompetence. Live vaccines generally should be deferred until immune function has improved. Inactivated vaccines administered during the period of altered immunocompetence might need to be repeated after immune function has improved. Finally, persons with altered immunocompetence might be at increased risk for an adverse reaction after administration of live-attenuated vaccines because of reduced ability to mount an effective immune response.

The degree of altered immunocompetence in a patient should be determined by a physician. The challenge for clinicians and other health-care providers is in assessing the safety and effectiveness of vaccines for conditions associated with primary or secondary immunodeficiency, especially when new therapeutic modalities are being used and information about the safety and effectiveness of vaccines has not been characterized fully in persons receiving these drugs (Table 11). Laboratory studies can be useful for assessing the effects of a disease or drug on the immune system. Tests useful to assess humoral immunity include immunoglobulin (and immunoglobulin subset) levels and specific antibody levels (tetanus, diphtheria, and response to pneumococcal vaccine). Tests that demonstrate the status of cellular immunity include lymphocyte numbers (i.e., a complete blood count with differential), a test that delineates concentrations and proportions of lymphocyte subsets (i.e., B and T-lymphocytes, CD4+ versus CD8+ lymphocytes), and tests that measure T-lymphocyte proliferation in response to specific or nonspecific stimuli (e.g., lymphocyte proliferation assays) (*114–115*). The ability to characterize a drug or disease condition as affecting cellular or humoral immunity is only the first step; using this information to draw inferences about whether particular vaccines are indicated or whether caution is advised with use of live or

TABLE 11. Vaccination of persons with primary and secondary immune deficiencies

Category	Specific immunodeficiency	Contraindicated vaccines*	Risk-specific recommended vaccines*	Effectiveness and comments
Primary				
B-lymphocyte (humoral)	Severe antibody deficiencies (e.g., X-linked agammaglobulinemia and common variable immunodeficiency)	Oral poliovirus (OPV)† Smallpox Live-attenuated influenza vaccine (LAIV) BCG Ty21a (live oral typhoid)	Pneumococcal Influenza (TIV) Consider measles and varicella vaccination	The effectiveness of any vaccine will be uncertain if it depends only on the humoral response; intravenous immune globulin interferes with the immune response to measles vaccine and possibly varicella vaccine
	Less severe antibody deficiencies (e.g., selective IgA deficiency and IgG subclass deficiency)	OPV† Other live-vaccines appear to be safe	Pneumococcal Influenza (TIV)	All vaccines probably effective. Immune response may be attenuated
T-lymphocyte (cell-mediated and humoral)	Complete defects (e.g., severe combined immunodeficiency [SCID] disease, complete DiGeorge syndrome)	All live vaccines §,¶	Pneumococcal Influenza (TIV)	Vaccines may be ineffective
	Partial defects (e.g., the majority of patients with DiGeorge syndrome, Wiskott-Aldrich syndrome, ataxia- telangiectasia)	All live vaccines §,¶	Pneumococcal Meningococcal *Haemophilus influenza* type b (Hib) (if not administered in infancy) Influenza (TIV)	Effectiveness of any vaccine depends on degree of immune suppression
Complement	Deficiency of early components (C1, C2, C3, and C4)	None	Pneumococcal Meningococcal Influenza (TIV)	All routine vaccines probably effective
	Deficiency of late components (C5-C9) and C3, properdin, factor B	None	Pneumococcal Meningococcal Influenza (TIV)	All routine vaccines probably effective
Phagocytic function	Chronic granulomatous disease, leukocyte adhesion defect, and myeloperoxidase deficiency	Live bacterial vaccines§	Pneumococcal** Influenza (TIV) (to decrease secondary bacterial infection)	All inactivated vaccines safe and probably effective Live viral vaccines probably safe and effective
Secondary				
	Human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS)	OPV Smallpox BCG LAIV Withhold MMR and varicella in severely immunocompromised persons	Influenza (TIV) Pneumococcal Consider Hib (if not administered in infancy) and meningococcal vaccination.	Measles, mumps, rubella (MMR, varicella, and all inactivated vaccines, including inactivated influenza, might be effective††
	Malignant neoplasm, transplantation, immunosuppressive or radiation therapy	Live viral and bacterial, depending on immune status	Influenza (TIV) Pneumococcal	Effectiveness of any vaccine depends on degree of immune suppression

Please note: *Errata have been published for this article. To view the errata, please click here and here.*

TABLE 11. (*Continued*) Vaccination of persons with primary and secondary immune deficiencies

Category	Specific immunodeficiency	Contraindicated vaccines*	Risk-specific recommended vaccines*	Effectiveness and comments
Secondary				
	Asplenia	None	Pneumococcal Meningococcal Hib (if not administered in infancy)	All routine vaccines probably effective.
	Chronic renal disease	LAIV	Pneumococcal Influenza (TIV) Hepatitis B	All routine vaccines probably effective.

* Other vaccines that are universally or routinely recommended should be administered if not contraindicated.
† OPV is no longer available for routine use in the United States.
§ Live bacterial vaccines: BCG, and Ty21a *Salmonella typhi* vaccine.
¶ Live viral vaccines: MMR, OPV, LAIV, yellow fever, and varicella, including MMRV and HZ vaccine, and vaccinia (smallpox). Smallpox vaccine is not recommended for children or the general public.
** Pneumococcal vaccine is not indicated for children with chronic granulomatous disease.
†† HIV-infected children should receive IG after exposure to measles, and can receive varicella and measles vaccine if CD4+ lymphocyte count is >15%.
Modified from American Academy of Pediatrics. Passive Immunization. In: Pickering LK, ed. Red Book: 2006 Report of the Committee on Infectious Diseases. 27th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2006, and CDC. Use of vaccines and immune globulins in persons with altered immunocompetence: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1993:42 (No. RR-4).

inactivated vaccines is more complicated and might require consultation with an infectious disease or immunology specialist.

Altered Immunocompetence as an Indication to Receive a Vaccine

Persons with altered immunocompetence generally are advised to receive TIV and polysaccharide-based vaccines (i.e., PCV, PPV, MCV4, MPSV, and Hib vaccines) on the basis of demonstrated effectiveness and an increased risk for disease if the vaccine is withheld.

Pneumococcal Vaccines

Two types of vaccine against invasive pneumococcal disease are available in the United States: PCV and PPV. PCV is routinely recommended for all children beginning at age 2 months. PCV is not recommended for persons aged >59 months. PPV is approved for persons aged ≥2 years with certain underlying medical conditions (including altered immunocompetence) and routinely for persons aged ≥65 years. Complete recommendations on use of PCV and PPV are available in the Recommended Child and Adolescent Immunization Schedule and the Recommended Adult Immunization Schedule (*113,116*).

Influenza Vaccine

Two types of influenza vaccine are available in the United States: TIV and LAIV. Vaccination with TIV is indicated specifically for persons with altered immunocompetence, including HIV infection. LAIV usually is contraindicated for persons with altered immunocompetence, although healthy persons with anatomic or functional asplenia and household and other close contacts of persons with altered immunocompetence can receive this vaccine.

Meningococcal Vaccine

Two types of meningococcal vaccine are available in the United States: MCV4 and MPSV. Persons with asplenia, C3 complement deficiency (*117*), or terminal complement component deficiency are at increased risk for meningococcal disease and should receive MCV4 or MPSV. Persons with HIV infection can elect to receive MCV4 or MPSV. MCV4 is licensed for persons aged 11–55 years[††]; children aged 2–10 years or persons aged ≥56 years should receive MPSV.

Haemophilus influenzae type b Vaccine

Hib conjugate vaccines are available in single or combined antigen preparations. Hib vaccine is recommended routinely for all children through age 59 months. However, a single dose of Hib vaccine also can be considered for asplenic older children, adolescents, and adults who did not receive the vaccine series in childhood. Clinicians and other health-care providers might consider use of Hib vaccine among persons with HIV infection who did not receive the vaccine as an infant or in childhood (*112*).

[††]A supplement to the original MCV4 vaccine Biologics License Agreement was submitted to FDA in March 2005, for use of MCV4 in children aged 2–10 years.

Vaccination of Contacts of Persons with Altered Immunocompetence

Household and other close contacts of persons with altered immunocompetence should receive all age-appropriate vaccines, with the exception of live OPV and smallpox vaccine. MMR, varicella, and rotavirus vaccines should be administered to susceptible household and other close contacts of immunocompromised patients when indicated. MMR vaccine viruses are not transmitted to contacts, and transmission of varicella vaccine is rare (*6,118*). No special precautions are needed unless the varicella vaccine recipient has a rash after vaccination, in which case direct contact with susceptible household contacts should be avoided until the rash resolves (*8,119*). To minimize potential rotavirus transmission, all members of the household should employ hand hygiene measures after contact with feces of a rotavirus-vaccinated infant for at least 1 week (*19*). Household and other close contacts of persons with altered immunocompetence should receive annual influenza vaccination. LAIV can be administered to otherwise eligible contacts (*47*).

Vaccination with Inactivated Vaccines

All inactivated vaccines can be administered safely to persons with altered immunocompetence whether the vaccine is a killed whole organism or a recombinant, subunit, toxoid, polysaccharide, or polysaccharide protein-conjugate vaccine. If inactivated vaccines are indicated for persons with altered immunocompetence, the usual doses and schedules are recommended. However, the effectiveness of such vaccinations might be suboptimal.

Except for influenza vaccine, which should be administered annually (*47*), vaccination during chemotherapy or radiation therapy should be avoided if possible because antibody response might be suboptimal. However, administration of inactivated vaccines during chemotherapy or radiation is not contraindicated. Patients vaccinated within 2 weeks before starting immunosuppressive therapy or while receiving immunosuppressive therapy should be considered unvaccinated and should be revaccinated at least 3 months after therapy is discontinued if immune competence has been restored.

Vaccination with Live-Attenuated Vaccines

Severe complications have followed vaccination with live-attenuated viral and live-attenuated bacterial vaccines among persons with altered immunocompetence (*120–127*). Persons with most forms of altered immunocompetence should not receive live vaccines (MMR, varicella vaccine, LAIV, yellow fever vaccine, oral typhoid, BCG, and rotavirus) except in certain circumstances. Patients with leukemia, lymphoma, or other malignancies whose disease is in remission and whose chemotherapy has been terminated for at least 3 months can receive live-virus vaccines.

Children with defects in phagocyte function (e.g., chronic granulomatous disease or myeloperoxidase deficiency) can receive live-attenuated viral vaccines in addition to inactivated vaccines, but should not receive live-attenuated bacterial vaccines (e.g., BCG and Ty21a oral typhoid vaccine). Children with deficiencies in complement or with asplenia can receive live-attenuated viral and live-attenuated bacterial vaccines (*94*).

Persons with severe cell-mediated immune deficiency should not receive live attenuated vaccines. However, children with HIV infection are at increased risk for complications of primary varicella and herpes zoster compared with immunocompetent children (*118,128*). Limited data among HIV-infected children (specifically CDC class N1, N2, A1, A2, B1, or B2) with age-specific $CD4^+$ lymphocyte percentages of >15% indicate that varicella vaccine is immunogenic, effective, and safe (*129*). Varicella vaccine should be considered for children meeting these criteria. Eligible children should receive 2 doses of varicella vaccine with a 3-month interval between doses (*118*).

Persons with HIV infection are at increased risk for severe complications if infected with measles. No severe or unusual adverse events have been reported after measles vaccination among HIV-infected persons who did not have evidence of severe immunosuppression (*130–133*). Therefore, MMR vaccination is recommended for all asymptomatic HIV-infected persons who do not have evidence of severe immunosuppression (age-specific $CD4^+$ lymphocyte percentages of >15%) and for whom measles vaccination would otherwise be indicated. Similarly, MMR vaccination should be considered for mildly symptomatic (Pediatric Category A1, A2 or Adolescent/adult Category A) (*129,134*) HIV-infected persons who do not have evidence of severe immunosuppression (age-specific CD4+ lymphocyte percentages of >15%) for whom measles vaccination would otherwise be indicated.

HIV-infected persons who are receiving regular doses of IGIV might not respond to varicella vaccine or MMR or its individual component vaccines because of the continued presence of passively acquired antibody. However, because of the potential benefit, MMR and varicella vaccines should be considered approximately 2 weeks before the next scheduled dose of IGIV (if not otherwise contraindicated), although an optimal immune response might not occur depending on the dose and interval since the previous dose of IGIV. Unless serologic testing indicates that specific antibodies have been produced,

vaccination should be repeated (if not otherwise contraindicated) after the recommended interval (Table 4). An additional dose of IGIV should be considered for persons on maintenance IGIV therapy who are exposed to measles or varicella 3 or more weeks after administering a standard dose (100–400 mg/kg body weight) of IGIV.

Persons with impaired humoral immunity (e.g., hypogammaglobulinemia or dysgammaglobulinemia) should receive varicella vaccine (*118,135*). However, the majority of persons with these disorders also receive periodic doses of IGIV. Appropriate spacing should be maintained between administration of IGIV and varicella vaccine to prevent an inadequate response to vaccination caused by the presence of neutralizing antibodies from the IGIV. Household and other close contacts of persons with altered immunocompetence should receive all age appropriate vaccines, with the exception of live OPV and smallpox vaccine.

Recipients of Hematopoietic Stem Cell Transplant

Hematopoietic stem cell transplantation (HSCT) results in immunosuppression from the hematopoietic ablative therapy preceding transplant, from drugs used to prevent or treat graft-versus-host disease, and in certain cases from the underlying disease process necessitating transplantation (*136*). HSCT involves ablation of the bone marrow with reimplantation of the person's own stem cells or stem cells from a donor. Antibody titers to vaccine-preventable diseases (e.g., tetanus, poliovirus, measles, mumps, rubella, and encapsulated bacteria) decline 1–4 years after autologous or allogeneic HSCT if the recipient is not revaccinated. HSCT recipients of all ages are at increased risk for certain vaccine-preventable diseases, including diseases caused by encapsulated bacteria (i.e., pneumococcal, meningococcal, and Hib infections). As a result, HSCT recipients should be revaccinated routinely after HSCT, regardless of the source of the transplanted stem cells (*136*). Revaccination with inactivated vaccines should begin 12 months after HSCT, except inactivated influenza vaccine, which should be administered beginning at least 6 months after HSCT and annually thereafter for the life of the patient. PPV should be administered at 12 and 24 months after HSCT. Data are limited about the use of heptavalent PCV in this population. Sequential administration of 2 doses of heptavalent pneumococcal conjugate vaccine followed by a dose of pneumococcal polysaccharide vaccine (with 8 weeks between doses) can be considered, especially for children aged <60 months. A 3-dose regimen of Hib vaccine should be administered at ages 12, 14, and 24 months after transplantation for all age groups (*136*). MMR vaccine should be administered 24 months after transplantation if the HSCT recipient is immunocompetent. Because of insufficient experience using varicella vaccine among HSCT recipients, physicians should assess the immune status of each recipient on a case-by-case basis and determine the risk for infection before using these vaccines. If a decision is made to vaccinate with varicella vaccine, the vaccine should be administered a minimum of 24 months after transplantation if the HSCT recipient is presumed to be immunocompetent (*137*).

Situations in Which Some Degree of Immunodeficiency Might be Present

Asplenia and use of corticosteroids or certain drugs have the potential to be immunosuppressive and in each, some degree of altered immunocompetence is presumed to exist.

Anatomic or Functional Asplenia

Persons with anatomic (e.g., surgical removal or congenital absence) or functional (as occurs with sickle cell disease) asplenia are at increased risk for infection by encapsulated bacteria, especially with *S. pneumoniae* (pneumococcus), *N. meningitidis* (meningococcus), and Hib (*26,48,117*). Persons with anatomic or functional asplenia should receive pneumococcal vaccine, depending on their age and previous pneumococcal vaccination status, as recommended (*29,48,113,116*).

Meningococcal vaccine is recommended for persons with anatomic or functional asplenia. Children aged 2–10 years and persons aged ≥56 years should receive MPSV. MCV4 is approved for persons aged 11–55 years[††] and is preferred for persons in this age group, but MPSV is an acceptable alternative (*117*). A second dose of MPSV can be considered at least 5 years after the initial dose. The duration of immunity after MCV4 is not known, but is thought to be long-lasting like other conjugate vaccines, and revaccination is not recommended.

No efficacy data are available on which to base a recommendation about use of Hib vaccine for older children and adults with the chronic conditions associated with an increased risk for Hib disease. However, studies suggest good immunogenicity in patients who have sickle cell disease or have had splenectomies; administering Hib vaccine to these patients is not contraindicated (*112*).

Pneumococcal, meningococcal, and Hib vaccines should be administered at least 2 weeks before elective splenectomy, if possible. If vaccines are not administered before surgery, they should be administered as soon as the person's condition stabilizes after the procedure.

Please note: Errata have been published for this article. To view the errata, please click here and here.

Corticosteroids

The amount of systemically absorbed corticosteroids and the duration of administration needed to suppress the immune system of an otherwise immunocompetent person are not well defined. Corticosteroid therapy usually is not a contraindication to administering live-virus vaccine when administration is short-term (i.e., <2 weeks); a low-to-moderate dose (<20 mg or prednisone or equivalent per day); long-term, alternate-day treatment with short-acting preparations; maintenance physiologic doses (replacement therapy); or administered topically (skin or eyes), inhaled, or by intra-articular, bursal, or tendon injection (*138*). No evidence of increased severity of reactions to live-attenuated vaccines has been reported among persons receiving corticosteroid therapy by aerosol, and such therapy is not a reason to delay vaccination. The immunosuppressive effects of steroid treatment vary, but the majority of clinicians consider a dose equivalent to either >2 mg/kg of body weight or 20 mg/day of prednisone or equivalent for persons who weigh >10 kg when administered for ≥2 weeks as sufficiently immunosuppressive to raise concern about the safety of vaccination with live-virus vaccines (*112,138*). Corticosteroids used in greater than physiologic doses also can reduce the immune response to vaccines. Vaccination providers should wait at least 1 month after discontinuation of high dose systemically absorbed corticosteroid therapy administered for more than 2 weeks before administering a live-virus vaccine.

Other Immunosuppressive Drugs

Whenever feasible, clinicians should provide all indicated vaccines to all persons before initiation of chemotherapy, before treatment with other immunosuppressive drugs, and before radiation or splenectomy. Persons receiving chemotherapy or radiation for leukemia and other hematopoetic malignancies, solid tumors, or after solid organ transplant should be assumed to have altered immunocompetence. Live-attenuated vaccines should not be administered for at least 3 months after such immunosuppressive therapy. Inactivated vaccines administered during chemotherapy might need to be readministered after immune competence is regained. Persons vaccinated before chemotherapy for leukemia, lymphoma, other malignancies, or radiation generally are thought to retain immune memory after treatment, although revaccination following chemotherapy for acute lymphoblastic leukemia might be indicated (*139*). Revaccination of a person after chemotherapy or radiation therapy is not thought to be necessary if the previous vaccination occurred before therapy and not during the therapy, with the exception of recipients of HSCT, who should be revaccinated as recommended previously. Determination of the level of immune memory and the need for revaccination should be made by the treating physician.

Inactivated vaccines can be administered during low dose intermittent or maintenance therapy of immunosuppressive drugs. The safety and efficacy of live-attenuated vaccines during such therapy is unknown. Physicians should carefully weigh the risks for and benefits of providing injectable live vaccines to adult patients on low-dose therapies for chronic autoimmune disease. The safety and efficacy of live-attenuated vaccines administered concurrently with recombinant human immune mediators and immune modulators is unknown. Evidence that use of therapeutic monoclonal antibodies, especially the antitumor necrosis factor agents adalimumab, infliximab, and etanercept, causes reactivation of latent tuberculosis infection and tuberculosis disease and predisposes to other opportunistic infections suggests caution in the use of live vaccines in patients receiving these drugs (*105–110*). Until additional information becomes available, avoidance of live attenuated vaccines during intermittent or low dose chemotherapy or other immunosuppressive therapy is prudent, unless the benefit of vaccination outweighs the hypothetical increased risk for an adverse reaction after vaccination.

Special Situations

Concurrently Administering Antimicrobial Agents and Vaccines

With limited exceptions, using an antimicrobial agent is not a contraindication to vaccination. Antimicrobial agents have no effect on the response to live-attenuated vaccines, except live oral Ty21a typhoid vaccine, and have no effect on inactivated, recombinant subunit, or polysaccharide vaccines or toxoids. Ty21a typhoid vaccine should not be administered to persons receiving antimicrobial agents until 24 hours after any dose of antimicrobial agent (*20*).

Antiviral drugs used for treatment or prophylaxis of influenza virus infections have no effect on the response to inactivated influenza vaccine (*47*). However, live-attenuated influenza vaccine should not be administered until 48 hours after cessation of therapy using antiviral influenza drugs. If feasible, antiviral medication should not be administered for 2 weeks after LAIV administration (*47*). Antiviral drugs active against herpesviruses (e.g., acyclovir or valacyclovir) might reduce the efficacy of live-attenuated varicella vaccine. These drugs should be discontinued at least 24 hours before administration of varicella-containing vaccines, if possible.

The antimalarial drug mefloquine could affect the immune response to oral Ty21a typhoid vaccine if both are taken si-

multaneously (*140*). To minimize this effect, administering Ty21a typhoid vaccine at least 24 hours before or after a dose of mefloquine is prudent.

Tuberculosis Screening and Skin Test Reactivity

Measles illness, severe acute or chronic infections, HIV infection, and malnutrition can create a relatively anergic state during which the tuberculin skin test (TST) (previously referred to as purified protein derivative [PPD] skin test) might give a false negative reaction (*141–143*). Although any live attenuated measles vaccine can theoretically suppress TST reactivity, the degree of suppression is probably less than that occurring from acute infection from wild-type measles virus. Although routine TST screening of all children is no longer recommended, TST screening is sometimes needed at the same time as administering a measles-containing vaccine (e.g., for well-child care, school entrance, or for employee health reasons).

TST and measles-containing vaccine can be administered at the same visit (preferred option). Simultaneously administering TST and measles-containing vaccine does not interfere with reading the TST result at 48–72 hours and ensures that the person has received measles vaccine.

If the measles-containing vaccine has been administered recently, TST screening should be delayed for at least 4 weeks after vaccination. A delay in performing TST will remove the concern of any theoretical but transient suppression of TST reactivity from the vaccine.

TST screening can be performed and read before administering the measles-containing vaccine. This option is the least favored because it will delay receipt of the measles-containing vaccine.

No data exist for the potential degree of TST suppression that might be associated with other injectable, live-attenuated virus vaccines (e.g., varicella and yellow fever). However, in the absence of data, following guidelines for measles-containing vaccine when scheduling TST screening and administering other live-attenuated virus vaccines is prudent. If the opportunity to vaccinate might be missed, vaccination should not be delayed only because of these theoretical considerations. Because of similar concerns about smallpox vaccine and TST suppression, a TST should not be performed until four weeks after smallpox vaccination (*144*).

TST reactivity in the absence of tuberculosis disease is not a contraindication to administration of any vaccine, including live-attenuated virus vaccines. Tuberculosis disease is not a contraindication to vaccination, unless the person is moderately or severely ill. Although no studies have reported the effect of MMR vaccine on persons with untreated tuberculosis, a theoretical basis exists for concern that measles vaccine might exacerbate the disease tuberculosis (*6*). As a result, before administering MMR to persons with untreated active tuberculosis, initiating antituberculosis therapy is advisable (*7*). Considering if concurrent immunosuppression (e.g., immunosuppression caused by HIV infection) is a concern before administering live attenuated vaccines also is prudent.

Severe Allergy to Vaccine Components

Vaccine components can cause allergic reactions among certain recipients. These reactions can be local or systemic and can include mild-to-severe anaphylaxis or anaphylactic-like responses (e.g., generalized urticaria or hives, wheezing, swelling of the mouth and throat, difficulty breathing, hypotension, and shock). Allergic reactions might be caused by the vaccine antigen, residual animal protein, antimicrobial agents, preservatives, stabilizers, or other vaccine components (*145*). Components of each vaccine are listed in the respective package insert. An extensive listing of vaccine components, their use, and the vaccines that contain each component has been published *(146)* and is also available from CDC's National Center for Immunization and Respiratory Diseases (proposed) (http://www.cdc.gov/nip).

The most common animal protein allergen is egg protein, which is found in influenza and yellow fever vaccines, which are prepared using embryonated chicken eggs. Ordinarily, persons who are able to eat eggs or egg products safely can receive these vaccines; persons with histories of anaphylactic or anaphylactic-like allergy to eggs or egg proteins should generally not receive these vaccines. Asking persons if they can eat eggs without adverse effects is a reasonable way to determine who might be at risk for allergic reactions from receiving yellow fever and influenza vaccines. A regimen for administering influenza vaccine to children with egg hypersensitivity and severe asthma has been developed (*147*).

Measles and mumps vaccine viruses are grown in chick embryo fibroblast tissue culture. Persons with a serious egg allergy can receive measles- or mumps-containing vaccines without skin testing or desensitization to egg protein (*6*). Rubella and varicella vaccines are grown in human diploid cell cultures and can safely be administered to persons with histories of severe allergy to eggs or egg proteins. The rare serious allergic reactions after measles or mumps vaccination or MMR are not believed to be caused by egg antigens, but to other components of the vaccine (e.g., gelatin) (*148–151*). MMR, MMRV, and their component vaccines and other vaccines contain hydrolyzed gelatin as a stabilizer. Extreme caution should be used when administering vaccines that contain

gelatin to persons who have a history of an anaphylactic reaction to gelatin or gelatin-containing products. Before administering gelatin-containing vaccines to such persons, skin testing for sensitivity to gelatin can be considered. However, no specific protocols for this approach have been published.

Certain vaccines contain trace amounts of antimicrobial agents or other preservatives (e.g., neomycin or thimerosal) to which patients might be severely allergic. The information provided in the vaccine package insert should be reviewed carefully before deciding if the rare patient with such allergies should receive the vaccine. No licensed vaccine contains penicillin or penicillin derivatives.

Certain vaccines contain trace amounts of neomycin. Persons who have experienced anaphylactic reactions to neomycin should not receive these vaccines. Most often, neomycin allergy is a contact dermatitis, a manifestation of a delayed type (cell-mediated) immune response, rather than anaphylaxis (*152,153*). A history of delayed type reactions to neomycin is not a contraindication for administration of these vaccines.

Thimerosal is an organic mercurial compound in use since the 1930s and is added to certain immunobiologic products as a preservative. A joint statement issued by the U.S. Public Health Service and the American Academy of Pediatrics (AAP) in 1999 (*154*) and agreed to by the American Academy of Family Physicians (AAFP) later in 1999, established the goal of removing thimerosal as soon as possible from vaccines routinely recommended for infants. Although no evidence exists of any harm caused by low levels of thimerosal in vaccines and the risk was only theoretical (*155*), this goal was established as a precautionary measure.

The public is concerned about the health effects of mercury exposure of any type, and the elimination of mercury from vaccines was judged a feasible means of reducing an infant's total exposure to mercury in a world where other environmental sources of exposure are more difficult or impossible to eliminate (e.g., common foods like tuna). Since mid-2001, vaccines routinely recommended for infants have been manufactured without thimerosal as a preservative. Live-attenuated vaccines have never contained thimerosal. Thimerosal-free formulations of inactivated influenza vaccine are available. Inactivated influenza vaccine also is available in formulations with trace thimerosal, in which thimerosal no longer functions as a preservative, and in formulations that contain thimerosal. Thimerosal that acts as a preservative is present in certain other vaccines that can be administered to children (e.g., Td and DT). Information about the thimerosal content of vaccines is available from FDA (http://www.fda.gov/cber/vaccine/thimerosal.htm).

Receiving thimerosal-containing vaccines might lead to induction of allergy. However, limited scientific basis exists for this assertion (*145*). Allergy to thimerosal usually consists of local delayed type hypersensitivity reactions (*156–158*). Thimerosal elicits positive delayed type hypersensitivity patch tests in 1%–18% of persons tested, but these tests have limited or no clinical relevance (*159–160*). The majority of persons do not experience reactions to thimerosal administered as a component of vaccines even when patch or intradermal tests for thimerosal indicate hypersensitivity (*160*). A localized or delayed type hypersensitivity reaction to thimerosal is not a contraindication to receipt of a vaccine that contains thimerosal.

Latex Allergy

Latex is sap from the commercial rubber tree. Latex contains naturally occurring impurities (e.g., plant proteins and peptides) that might be responsible for allergic reactions. Latex is processed to form natural rubber latex and dry natural rubber. Dry natural rubber and natural rubber latex might contain the same plant impurities as latex but in lesser amounts. Natural rubber latex is used to produce medical gloves, catheters, and other products. Dry natural rubber is used in syringe plungers, vial stoppers, and injection ports on intravascular tubing. Synthetic rubber and synthetic latex also are used in medical gloves, syringe plungers, and vial stoppers. Synthetic rubber and synthetic latex do not contain natural rubber or natural latex and do not contain the impurities linked to allergic reactions. Latex or dry natural rubber used in vaccine packaging is generally noted in the manufacturer's package insert.

The most common type of latex sensitivity is contact-type (type 4) allergy, usually as a result of prolonged contact with latex-containing gloves (*161*). However, injection-procedure–associated latex allergies among patients with diabetes mellitus have been described (*162–164*). Allergic reactions (including anaphylaxis) after vaccination procedures are rare (*165*). Only one known report of an allergic reaction after administering HepB to a patient with known severe allergy (anaphylaxis) to latex has been published (*166*).

If a person reports a severe (anaphylactic) allergy to latex, vaccines supplied in vials or syringes that contain natural rubber should not be administered unless the benefit of vaccination outweighs the risk for a potential allergic reaction. For latex allergies other than anaphylactic allergies (e.g., a history of contact allergy to latex gloves), vaccines supplied in vials or syringes that contain dry natural rubber or natural rubber latex can be administered.

Vaccination of Preterm Infants

In the majority of cases, infants born prematurely, regardless of birthweight, should be vaccinated at the same chronological age and according to the same schedule and precautions as full-term infants and children. Birthweight and size are not factors in deciding whether to postpone routine vaccination of a clinically stable preterm infant (*167–171*), except for HepB. The full recommended dose of each vaccine should be used. Divided or reduced doses are not recommended (*173*).

Decreased seroconversion rates might occur among certain preterm infants with low birthweights (i.e., <2,000 g) after administration of HepB at birth (*173*). However, by chronological age 1 month, all preterm infants, regardless of initial birth weight or gestational age, are likely to respond as adequately as older and larger infants (*174–176*). Preterm infants born to HBsAg-positive mothers and mothers with unknown HBsAg status must receive immunoprophylaxis with HepB and HBIG within 12 hours after birth. If these infants weigh <2,000 g at birth, the initial vaccine dose should not be counted towards completion of the HepB series, and 3 additional doses of HepB should be administered, beginning when the infant is aged 1 month. Preterm infants weighing <2,000 g and born to HBsAg-negative mothers should receive the first dose of the HepB series at chronological age 1 month or at hospital discharge. (*30*)

Breast Feeding and Vaccination

Neither inactivated nor live vaccines administered to a lactating woman affect the safety of breast feeding for women or their infants. Breast feeding does not adversely affect immunization and is not a contraindication for any vaccine, with the exception of smallpox vaccine. Limited data indicate that breast feeding can enhance the response to certain vaccine antigens (*177*). Breast-fed infants should be vaccinated according to recommended schedules (*178–180*).

Although live vaccines multiply within the mother's body, the majority have not been demonstrated to be excreted in human milk (*181*). Although rubella vaccine virus might be excreted in human milk, the virus usually does not infect the infant. If infection does occur, it is well-tolerated because the virus is attenuated (*182*). Inactivated, recombinant, subunit, polysaccharide, conjugate vaccines and toxoids pose no risk for mothers who are breast feeding or for their infants.

Vaccination During Pregnancy

Risk for a developing fetus from vaccination of the mother during pregnancy primarily is theoretical. No evidence exists of risk from vaccinating pregnant women with inactivated virus or bacterial vaccines or toxoids (*183,184*). Live vaccines pose a theoretical risk to the fetus. Benefits of vaccinating pregnant women usually outweigh potential risks when the likelihood of disease exposure is high, when infection would pose a risk to the mother or fetus, and when the vaccine is unlikely to cause harm.

Recommendations for vaccination during pregnancy can be found in the adult immunization schedule (*113*). Pregnant women should receive Td vaccine if indicated. Previously vaccinated pregnant women who have not received a Td vaccination within the last 10 years should receive a booster dose. Pregnant women who are not vaccinated or only partially immunized against tetanus should complete the primary series (*28,112*). Women for whom the vaccine is indicated but who have not completed the recommended 3-dose series during pregnancy should receive follow-up after delivery to ensure the series is completed. Pregnant adolescents and adults who received the last tetanus-containing vaccine <10 years previously are generally recommended to receive Tdap after delivery. To prevent neonatal tetanus, pregnant adolescents who received the last dose of tetanus-toxoid containing vaccine ≥10 years previously should generally receive Td in preference to Tdap while they are pregnant (*28*), although Tdap is not contraindicated during pregnancy.

Women in the second and third trimesters of pregnancy are at increased risk for hospitalization from influenza. Therefore, routine influenza vaccination is recommended for all women who will be pregnant (in any trimester) during influenza season (usually November–March in the United States) (*47*).

IPV can be administered to pregnant women who are at risk for exposure to wild-type poliovirus infection (*4*). HepB is recommended for pregnant women at risk for hepatitis B virus infection (*30*). HepA, pneumococcal polysaccharide, meningococcal conjugate, and meningococcal polysaccharide vaccines should be considered for women at increased risk for those infections (*48,117,185*). Pregnant women who must travel to areas where the risk for yellow fever is high should receive yellow fever vaccine because the limited theoretical risk from vaccination is substantially outweighed by the risk for yellow fever infection (*24,186*).

Pregnancy is a contraindication for smallpox (vaccinia), measles, mumps, rubella, and varicella-containing vaccines. Smallpox (vaccinia) vaccine is the only vaccine known to cause harm to a fetus when administered to a pregnant woman. In addition to the vaccinee herself, smallpox (vaccinia) vaccine should not be administered to a household contact of a pregnant woman (*144*). Although of theoretical concern, no cases of congenital rubella or varicella syndrome or abnormalities

attributable to fetal infection have been observed among infants born to susceptible women who received rubella or varicella vaccines during pregnancy (*6,187*). Because of the importance of protecting women of childbearing age against rubella and varicella, reasonable practices in any vaccination program include asking women if they are pregnant or might become pregnant in the next 4 weeks; not vaccinating women who state that they are or plan to be pregnant; explaining the theoretical risk for the fetus if MMR, varicella, or MMRV vaccine were administered to a women who is pregnant; and counseling women who are vaccinated not to become pregnant during the 4 weeks after MMR, varicella, or MMRV vaccination (*6,39,188*). Routine pregnancy testing of women of childbearing age before administering a live-virus vaccine is not recommended (*6*). If vaccination of an unknowingly pregnant woman occurs or if she becomes pregnant within 4 weeks after MMR or varicella vaccination, she should be counseled about the theoretical basis of concern for the fetus; however, MMR or varicella vaccination during pregnancy should not be regarded as a reason to terminate pregnancy (*6,8,189*).

Persons who receive MMR vaccine do not transmit the vaccine viruses to contacts (*6*). Transmission of varicella vaccine virus to contacts is extremely rare (*118*). MMR and varicella vaccines should be administered when indicated to the children and other household contacts of pregnant women (*6,8*).

All pregnant women should be evaluated for immunity to rubella and varicella and be tested for the presence of HBsAg in every pregnancy (*6,30,39*). Women susceptible to rubella and varicella should be vaccinated immediately after delivery. A woman found to be HBsAg-positive should be followed carefully to ensure that the infant receives HBIG and begins the hepatitis B vaccine series no later than 12 hours after birth and that the infant completes the recommended HepB vaccine series on schedule (*30*). No known risk exists for the fetus from passive immunization of pregnant women with immune globulin preparations.

Persons Vaccinated Outside the United States, Including Internationally Adopted Children

The ability of a clinician to determine that a person is protected on the basis of their country of origin and their records alone is limited. Vaccines administered outside the United States can generally be accepted as valid if the schedule was similar to that recommended in the United States (i.e., minimum ages and intervals). Only written documentation should be accepted as evidence of previous vaccination. Written records are more likely to predict protection if the vaccines, dates of administration, intervals between doses, and the person's age at the time of vaccination are comparable to U.S. recommendations. Although vaccines with inadequate potency have been produced in other countries (*190,191*), the majority of vaccines used worldwide is produced with adequate quality control standards and are potent.

The number of U.S. families adopting children from outside the United States has increased substantially in recent years (*192*). Adopted children's birth countries often have vaccination schedules that differ from the recommended childhood immunization schedule in the United States. Differences in the U.S. immunization schedule and those used in other countries include the vaccines administered, the recommended ages of administration, and the number and timing of doses.

Data are inconclusive about the extent to which an internationally adopted child's vaccination record reflects the child's protection. A child's record might indicate administration of MMR vaccine when only single-antigen measles vaccine was administered. A study of children adopted from orphanages in the People's Republic of China, Russia, and Eastern Europe determined that 67% of children with documentation of more than 3 doses of DTP before adoption had nonprotective titers to these antigens. By contrast, children adopted from these countries who received vaccination in the community (not only from orphanages) and who possessed records of 1 or more doses of DTP exhibited protective titers 67% of the time (*193*). However, antibody testing was performed by using a hemagglutination assay, which tends to underestimate protection and cannot directly be compared with antibody concentration (*194*). Data are likely to remain limited for countries other than the People's Republic of China, Russia, and Eastern Europe because of the limited number of adoptees from other countries.

Clinicians and other health-care providers can follow one of multiple approaches if a question exists about whether vaccines administered to an international adoptee were immunogenic. Repeating the vaccinations is an acceptable option. Doing so usually is safe and avoids the need to obtain and interpret serologic tests. If avoiding unnecessary injections is desired, judicious use of serologic testing might be helpful in determining which vaccinations are needed. For some vaccines, the most readily available serologic tests cannot document protection against infection. These recommendations provide guidance on possible approaches to evaluation and revaccination for each vaccine recommended universally for children in the United States (Table 12). Clinicians and other health-care providers should ensure that household contacts of internationally adoptees are adequately vaccinated, particularly for measles and hepatitis B.

TABLE 12. Approaches to the evaluation and vaccination of internationally adopted children with no or questionable vaccination records

Vaccine	Recommended approach	Alternative approach
Measles, mumps, and rubella (MMR)	Revaccinate with MMR	Serologic testing for immunoglobulin G (IgG) antibody to measles, mumps, and rubella
Haemophilus influenzae type b (Hib)	Age-appropriate revaccination	—
Hepatitis A	Age-appropriate revaccination	Serologic testing for IgG antibody to hepatitis A virus
Hepatitis B (Hep B)	Age-appropriate revaccination and serologic testing for HBsAg*	—
Poliovirus	Revaccinate with inactivated poliovirus vaccine (IPV)	Serologic testing for neutralizing antibody to poliovirus types 1, 2, and 3 (limited availability)
Diphtheria and tetanus toxoids and acellular pertussis (DTaP)	Revaccination with DTaP, with serologic testing for specific IgG antibody to tetanus and diphtheria toxins in the event of a severe local reaction	Children whose records indicate receipt of ≥3 doses: serologic testing for specific IgG antibody to diphtheria and tetanus toxins before administering additional doses (see text), or administer a single booster dose of DTaP, followed by serological testing after 1 month for specific IgG antibody to diphtheria and tetanus toxins with revaccination as appropriate
Varicella	Age-appropriate vaccination of children who lack evidence of varicella immunity	—
Pneumococcal conjugate	Age-appropriate vaccination	—

* Very rarely, Hep B vaccine can give a false positive HBsAg result up to 18 days following vaccination; therefore, blood should be drawn to test for HBsAg before vaccinating (CDC. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: Recommendations of the Advisory Committee on Immunization Practices [ACIP]; Part I: Immunization in Infants, Children, and Adolescents. MMWR 2005;54[No. RR-16]).

MMR Vaccine

The simplest approach to resolving concerns about MMR vaccination among internationally adopted children is to revaccinate with 1 or 2 doses of MMR vaccine, depending on the child's age. Serious adverse events after MMR vaccinations are rare (*6*). No evidence indicates that administering MMR vaccine increases the risk for adverse reactions among persons who are already immune to measles, mumps, or rubella as a result of previous vaccination or natural disease. Doses of measles-containing vaccine administered before the first birthday should not be counted as part of the series (*6*). Alternatively, serologic testing for immunoglobulin G (IgG) antibody to vaccine viruses indicated on the vaccination record can be considered. Serologic testing is widely available for measles and rubella IgG antibody. A child whose record indicates receipt of monovalent measles or measles-rubella vaccine on or after the first birthday and who has protective antibody against measles and rubella should receive 1 or 2 doses of MMR or MMRV as age-appropriate to ensure protection against mumps and varicella (and rubella if measles vaccine alone had been used). If a child whose record indicates receipt of MMR at age ≥12 months has a protective concentration of antibody to measles, no additional vaccination is needed unless required for school entry.

Hib Vaccine

Interpretation of a serologic test to verify protection from Hib bacteria for children vaccinated >2 months previously can be difficult to interpret. Because the number of vaccinations needed for protection decreases with age and adverse events are rare (*26*), age-appropriate vaccination should be provided. Hib vaccination is not recommended routinely for children aged ≥5 years (*116*).

Hepatitis A Vaccine

Children without documentation of HepA vaccination or serologic evidence of immunity should be vaccinated on arrival if aged ≥12 months (*185*).

Hepatitis B Vaccine

Children not known to be vaccinated for hepatitis B should receive an age-appropriate series of HepB. A child whose records indicate receipt of 3 or more doses of vaccine can be considered protected, and additional doses are not needed if 1 or more doses were administered at age ≥24 weeks. Chil-

dren who received their last HepB dose at age <24 weeks should receive an additional dose at age ≥24 weeks. Children who have received fewer than 3 doses of vaccine should complete the series at the recommended intervals and ages.

All foreign-born persons and immigrants, refugees, and internationally adopted children born in Asia, the Pacific Islands, Africa, and other regions in which HBV is highly endemic should be tested for HBsAg, regardless of vaccination status. Those determined to be HBsAg-positive should be monitored for development of liver disease. Household members of HBsAg-positive children or adults should be vaccinated if not already immune.

Poliovirus Vaccine

The simplest approach is to revaccinate internationally adopted children with IPV according to the U.S. schedule. Adverse events after IPV are rare (*4*). Children appropriately vaccinated with 3 doses of OPV in economically developing countries might have suboptimal seroconversion, including to type 3 poliovirus (*180*). Serologic testing for neutralizing antibody to poliovirus types 1, 2, and 3 can be obtained commercially and at certain state health department laboratories. Children with protective titers against all three types do not need revaccination and should complete the schedule as age-appropriate.

DTaP Vaccine

Vaccination providers can revaccinate a child with DTaP vaccine without regard to recorded doses; however, one concern about this approach is that data indicate increased rates of local adverse reactions after the fourth and fifth doses of DTP or DTaP (*46*). If a revaccination approach is adopted and a severe local reaction occurs, serologic testing for specific IgG antibody to tetanus and diphtheria toxins can be measured before administering additional doses. Protective concentration[§§] indicates that further doses are unnecessary and subsequent vaccination should occur as age-appropriate. No established serologic correlates exist for protection against pertussis.

For a child whose record indicates receipt of 3 or more doses of DTP or DTaP, serologic testing for specific IgG antibody to both diphtheria and tetanus toxin before additional doses is a reasonable approach. If a protective concentration is present, recorded doses can be considered valid, and the vaccination series should be completed as age-appropriate. Indeterminate antibody concentration might indicate immunologic memory but antibody waning; serology can be repeated after a booster dose if the vaccination provider wants to avoid revaccination with a complete series.

Alternately, for a child whose records indicate receipt of 3 or more doses, a single booster dose can be administered, followed by serologic testing after 1 month for specific IgG antibody to both diphtheria and tetanus toxins. If a protective concentration is obtained, the recorded doses can be considered valid and the vaccination series completed as age-appropriate. Children with indeterminate concentration after a booster dose should be revaccinated with a complete series.

Varicella Vaccine

Varicella vaccine is not administered in the majority of countries. A child who lacks reliable evidence of varicella immunity should be vaccinated as age-appropriate (*8,116*).

Pneumococcal Vaccines

PCV and PPV are not administered in the majority of countries and should be administered as age-appropriate or as indicated by the presence of underlying medical conditions (*29,48*).

Vaccinating Persons with Bleeding Disorders and Persons Receiving Anticoagulant Therapy

Because of the risk for hematoma formation after injections, intramuscular injections are often avoided among persons with bleeding disorders by using the subcutaneous or intradermal routes for vaccines that are administered normally by the intramuscular route. HepB administered intramuscularly to 153 persons with hemophilia by using a 23-gauge needle or smaller, followed by steady pressure to the site for 1–2 minutes, resulted in a 4% bruising rate with no patients requiring factor supplementation (*195*). Whether antigens that produce more local reactions (e.g., pertussis) would produce an equally low rate of bruising is unknown.

When HepB or any other intramuscular vaccine is indicated for a patient with a bleeding disorder or a person receiving anticoagulant therapy, the vaccine should be administered intramuscularly if, in the opinion of a physician familiar with the patient's bleeding risk, the vaccine can be administered with reasonable safety by this route. If the patient receives antihemophilia or similar therapy, intramuscular vaccinations can be scheduled shortly after such therapy is administered. A fine needle (23 gauge or smaller) should be used for the vaccination and firm pressure applied to the site, without rubbing, for at least 2 minutes. The patient or family should be instructed concerning the risk for hematoma from the injection.

[§§]Enzyme immunoassay tests are available. Physicians should contact the laboratory performing the test for interpretive standards and limitations. Protective concentrations for antibody to diphtheria and tetanus toxins are defined as ≥0.1 IU/mL.

Vaccination Records

Consent to Vaccinate

The National Childhood Vaccine Injury Act of 1986 (42 U.S.C. § 300aa-26) requires that all health-care providers in the United States who administer any vaccine covered by the Act[¶] must provide a copy of the relevant, current edition of the vaccine information materials that have been produced by CDC before administering each dose of the vaccine. Vaccine information statements (VIS) are available at http://www.cdc.gov/nip/publications/VIS/default.htm and http://www.immunize.org/vis. VIS must be provided to the parent or legal representative of any child or to any adult to whom the physician or other health-care provider intends to administer the vaccine. The act does not require that a signature be obtained, but documentation of consent is recommended or required by certain state or local authorities.

Provider Records

Documentation of patient vaccinations helps ensure that persons in need of a vaccine receive it and that adequately vaccinated patients are not administered excess doses, possibly increasing the risk for local adverse events (e.g., tetanus toxoid). Serologic test results for vaccine-preventable diseases (e.g., those for rubella screening and antibody to hepatitis B surface antigen) and documented episodes of adverse events also should be recorded in the permanent medical record of the vaccine recipient.

Health-care providers who administer vaccines covered by the National Childhood Vaccine Injury Act are required to ensure that the permanent medical record of the recipient (or a permanent office log or file) indicates the date the vaccine was administered; the vaccine manufacturer; the vaccine lot number; and the name, address, and title of the person administering the vaccine. In addition, the provider is required to record the edition date of the VIS distributed and the date those materials were provided. In the Act, the term health-care provider is defined as any licensed health-care professional, organization, or institution, whether private or public (including federal, state, and local departments and agencies), under whose authority a specified vaccine is administered. This same information should be kept for all vaccines, not just for those required by the National Childhood Vaccine Injury Act.

[¶]As of May 2006, vaccines covered by the act include diphtheria, tetanus, pertussis, measles, mumps, rubella, poliovirus, HepB, Hib, varicella, pneumococcal conjugate, HepA, trivalent inactivated influenza vaccine, and pentavalent RV.

Patients' Personal Records

Official childhood vaccination records have been adopted by every state, territory, and the District of Columbia to encourage uniformity of records and to facilitate assessment of vaccination status by schools and child care centers. The records also are key tools in vaccination education programs aimed at increasing parental and patient awareness of the need for vaccines. A permanent vaccination record card should be established for each newborn infant and maintained by the parent or guardian. In certain states, these cards are distributed to new mothers before discharge from the hospital. Using vaccination record cards for adolescents and adults also is encouraged. Standardized adult vaccination records are available at http://www.immunize.org.

Immunization Information Systems

IISs are confidential, population-based, computerized information systems that collect and consolidate vaccination data from multiple health-care providers within a geographic area. IISs are a critical tool that can increase and sustain increased vaccination coverage by consolidating vaccination records of children from multiple providers, generating reminder and recall vaccination notices for each child, and providing official vaccination forms and vaccination coverage assessments (*196*). A fully operational IIS also can prevent duplicate vaccinations, limit missed appointments, reduce vaccine waste, and reduce staff time required to produce or locate vaccination records or certificates. The National Vaccine Advisory Committee strongly encourages development of community- or state-based IISs and recommends that vaccination providers participate in these systems whenever possible (*196*). One of the national health objectives for 2010 is 95% participation of children aged <6 years in a fully operational population-based IIS (objective 20.1) (*197*).

Reporting Adverse Events after Vaccination

Modern vaccines are safe and effective; however, adverse events have been reported after administration of all vaccines (*91*). These events range from frequent, minor, local reactions to extremely rare, severe, systemic illness (e.g., anaphylaxis). Establishing evidence for cause-and-effect relations on the basis of case reports and case series alone is impossible because temporal association alone does not necessarily indicate causation. Unless the symptom or syndrome that occurs after vaccination is clinically or pathologically distinctive, more detailed epidemiologic studies to compare the incidence of

the event among vaccinees with the incidence among unvaccinated persons are necessary. Reporting adverse events to public health authorities, including serious events, is a key stimulus to developing studies to confirm or refute a causal association with vaccination. More complete information about adverse reactions to a specific vaccine is available in the ACIP recommendations for that vaccine and in a specific statement on vaccine adverse reactions (*91*).

The National Childhood Vaccine Injury Act requires health-care providers to report selected events occurring after vaccination to VAERS. Events for which reporting is required appear in the Reportable Events Table.*** Persons other than health-care providers also can report adverse events to VAERS. All clinically significant adverse events other than those that must be reported or that occur after administration of vaccines not covered by the Act also should be reported to VAERS, even if the physician or other health-care provider is uncertain they are related causally to vaccination. VAERS forms and instructions are available in the FDA Drug Bulletin by contacting VAERS (800-822-7967), or from the VAERS website (http://www.vaers.hhs.gov/vaers.htm).

National Vaccine Injury Compensation Program

The National Vaccine Injury Compensation Program, established by the National Childhood Vaccine Injury Act, is a no-fault system in which persons thought to have suffered an injury or death as a result of administration of a covered vaccine can seek compensation. The program became operational on October 1, 1988, and is intended as an alternative to civil litigation under the traditional tort system in that negligence need not be proven. Claims arising from covered vaccines must first be adjudicated through the program before civil litigation can be pursued.

The program relies on a Reportable Events Table listing the vaccines covered by the program and the injuries, disabilities, illnesses, and conditions (including death) for which compensation might be awarded. The table defines the time during which the first symptom or substantial aggravation of an injury must appear after vaccination. Successful claimants receive a legal presumption of causation if a condition listed in the table is proven, thus avoiding the need to prove actual causation in an individual case. Claimants also can prevail for conditions not listed in the table if they prove causation. Injuries after administration of vaccines not listed in the legislation authorizing the program are not eligible for compensation through the program. Additional information is available from the National Vaccine Injury Compensation Program, Health Resources and Services Administration, Parklawn Building, Room 11C-26, 5600 Fishers Lane, Rockville, MD 20857; telephone: 800-338-2382; Website: http://www.hrsa.gov/osp/vicp.

Persons wanting to file a claim for vaccine injury should contact the following: U.S. Court of Federal Claims, 717 Madison Place, N.W., Washington, DC 20005; telephone: 202-357-6400.

Benefit and Risk Communication

Parents, guardians, legal representatives, and adolescent and adult patients should be informed about the benefits of and risks for vaccines in understandable language. Opportunity for questions should be provided before each vaccination. Discussion of the benefits of and risks for vaccination is sound medical practice and is required by law.

The National Childhood Vaccine Injury Act requires that vaccine information materials be developed for each vaccine covered by the Act. These materials, known as Vaccine Information Statements, must be provided by all public and private vaccination providers each time a vaccine is administered. Copies of Vaccine Information Statements are available from state health authorities responsible for vaccination, or they can be obtained from CDC's National Center for Immunization and Respiratory Disease (proposed) website (http://www.cdc.gov/nip). Translations of Vaccine Information Statements into languages other than English are available from certain state vaccination programs and from the Immunization Action Coalition website (http://www.immunize.org).

Health-care providers should anticipate that certain parents or patients will question the need for or safety of vaccination, refuse certain vaccines, or even reject all vaccinations. A limited number of persons might have religious or personal objections to vaccinations. Others might want to enter into a dialogue about the risks for and benefits of certain vaccines. Having a basic understanding of how patients view vaccine risk and developing effective approaches in dealing with vaccine safety concerns when they arise is imperative for vaccination providers.

Each person understands and reacts to vaccine information on the basis of different factors, including previous experience, education, personal values, method of data presentation, perceptions of the risk for disease, perceived ability to control those risks, and their risk preference. Increasingly, through the media and nonauthoritative Internet sites, decisions about risk are based on inaccurate information. Only through direct dialogue with parents and by using available

***The Reportable Events Table can be obtained from the Vaccine Injury Compensation Program Internet site at http://vaers.hhs.gov/reportable.htm.

resources can health-care providers prevent acceptance of media reports and information from nonauthoritative Internet sites as scientific fact.

When a parent or patient initiates a discussion about a vaccine controversy, the health-care provider should discuss the specific concerns and provide factual information, using appropriate language. Effective, empathetic vaccine risk communication is essential in responding to misinformation and concerns, recognizing that for certain persons, risk assessment and decision-making are difficult and confusing. Certain vaccines might be acceptable to the resistant parent. Their concerns should then be addressed using the VIS and offering other resource materials (e.g., information available on the National Center for Immunization and Respiratory Diseases (proposed) website [http://www.cdc.gov/nip]).

Although a limited number of providers might exclude from their practice those patients who question or refuse vaccination, the more effective public health strategy is to identify common ground and discuss measures that need to be followed if the patient's decision is to defer vaccination. As part of a strong recommendation, health-care providers can reinforce key points about each vaccine, including safety, and emphasize risks encountered by unvaccinated children. Parents should be advised of state laws pertaining to school or child-care entry, which might require that unvaccinated children be excluded from school or child care during outbreaks. Documentation of these discussions in the patient's record, including the refusal to receive certain vaccines (i.e., informed refusal), might reduce any potential liability if a vaccine-preventable disease occurs in the unvaccinated patient.

Vaccination Programs

The best way to reduce vaccine-preventable diseases is to have a highly immune population. Universal vaccination is a critical part of quality health care and should be accomplished through routine and intensive vaccination programs implemented in physicians' offices and in public health clinics. Programs should be established and maintained in all communities to ensure vaccination of all children at the recommended age. In addition, appropriate vaccinations should be available for all adolescents and adults.

Physicians and other pediatric vaccination providers should adhere to the standards for child and adolescent vaccination practices (*1*). These standards define appropriate vaccination practices for both the public and private sectors. The standards provide guidance on practices that will result in eliminating barriers to vaccination. These include practices aimed at eliminating unnecessary prerequisites for receiving vaccinations, eliminating missed opportunities to vaccinate, improving procedures to assess vaccination needs, enhancing knowledge about vaccinations among parents and providers, and improving the management and reporting of adverse events. In addition, the standards address the importance of recall and reminder systems and using assessments to monitor clinic or office vaccination coverage levels. Physicians and other health-care providers should simultaneously administer as many vaccine doses as possible, as indicated on the Recommended Child and Adolescent Immunization Schedule (*116*).

Standards of practice also have been published to increase vaccination coverage among adults (*2*). These standards include ensuring vaccine availability, routine review of vaccination status, communicating risks for and benefits to the patient, using standing orders, and recommending simultaneous administration of all indicated doses according to the Recommended Adult Immunization Schedule (*113*).

Every visit to a physician or other health-care provider can be an opportunity to update a patient's vaccination status with needed vaccinations. Official health agencies should take necessary steps, including, when appropriate, developing and enforcing child care and school vaccination requirements, to ensure that students at all grade levels (including college) and children in day care centers are protected against vaccine-preventable diseases. Agencies also should encourage institutions (e.g., hospitals and long-term–care facilities) to adopt policies about the appropriate vaccination of patients, residents, and employees (*198*).

Dates of vaccination (day, month, and year) should be recorded on institutional vaccination records (e.g., records kept in schools and day care centers). These records will facilitate assessments that a primary vaccination series has been completed according to an appropriate schedule and that needed booster doses have been administered at the appropriate time.

The independent, nonfederal Task Force on Community Preventive Services (the Task Force), whose membership is appointed by CDC, provides public health decision-makers with recommendations on population-based interventions to promote health and prevent disease, injury, disability, and premature death. The recommendations are based on systematic reviews of the scientific literature about effectiveness and cost-effectiveness of these interventions. In addition, the Task Force identifies critical information about the other effects of these interventions and the applicability to specific populations and settings and the potential barriers to implementation. This information is available at http://www.thecommunityguide.org.

Beginning in 1996, the Task Force systematically reviewed published evidence on the effectiveness and cost-effectiveness

of population-based interventions to increase coverage of vaccines recommended for routine use among children, adolescents, and adults. A total of 197 articles were identified that evaluated a relevant intervention, met inclusion criteria, and were published during 1980–1997. Reviews of 17 specific interventions were published in 1999 (*199–202*). Using the results of their review, the Task Force made recommendations about the use of these interventions (*202*). Several interventions were identified and recommended on the basis of published evidence. The interventions and the recommendations are summarized in this report (Table 13).

Vaccine Information Sources

In addition to these general recommendations, other sources are available that contain specific and updated vaccine information.

CDC-INFO Contact Center

The CDC-INFO contact center is supported by CDC's National Center for Immunization and Respiratory Diseases (proposed) and provides public health-related information, including vaccination information, for health-care providers and the public, 24 hours a day, seven days a week (Telephone [English and Spanish]: 800-232-4636; Telephone [TTY]: 800-232-6348).

CDC's National Center for Immunization and Respiratory Diseases (proposed)

CDC's National Center for Immunization and Respiratory Diseases (proposed) website provides direct access to immunization recommendations of ACIP, vaccination schedules, vaccine safety information, publications, provider education and training, and links to other vaccination-related websites (http://www.cdc.gov/nip).

MMWR

ACIP recommendations regarding vaccine use, statements of vaccine policy as they are developed, and reports of specific disease activity are published by CDC in the *MMWR* series. Electronic subscriptions are free (http://www.cdc.gov/subscribe.html). Printed subscriptions are available at

Superintendent of Documents
U.S. Government Printing Office
Washington, D.C. 20402-9235
202-512-1800

TABLE 13. Summary of recommendations for interventions to improve coverage of vaccines recommended for routine use among children, adolescents, and adults*

Intervention	Recommendations
Interventions that increase community demand for immunization	
Client reminder or recall systems	Strongly recommended
Multicomponent interventions, including education	Strongly recommended
School, day care, and college-entry requirements	Recommended
Community education alone	Insufficient evidence
Clinic-based education	Insufficient evidence
Patient or family incentives or sanctions	Insufficient evidence
Client-held medical records	Insufficient evidence
Interventions that enhance access to vaccination services	
Reducing out-of-pocket costs	Strongly recommended
Enhancing access through the U.S. Department of Agriculture's Women, Infants, and Children program	Recommended
Home visits, outreach, and case management	Recommended
Enhancing access at day care centers	Insufficient evidence
Enhancing access at schools	Recommended
Expanding access in health-care settings	Recommended as part of multicomponent interventions only
Interventions that target providers	
Reminder or recall systems	Strongly recommended
Assessment and feedback	Strongly recommended
Standing orders	Strongly recommended
Provider education alone	Insufficient evidence

* Adapted from Task Force on Community Preventive Services. Recommendations regarding interventions to improve vaccination coverage in children, adolescents and adults. Am J Prev Med 2000;18:92–6, and Task Force on Community Preventive Services. Recommendations to improve targeted vaccination coverage among high-risk adults. Am J Prev Med 2005;28:231–7.

American Academy of Pediatrics (AAP)

Every 3 years, AAP issues the *Red Book: Report of the Committee on Infectious Diseases*, which contains a composite summary of AAP recommendations concerning infectious diseases and immunizations for infants, children, and adolescents (Telephone: 888-227-1770; Website: http://www.aap.org).

American Academy of Family Physicians (AAFP)

Information from the professional organization of family physicians is available at http://www.aafp.org.

Immunization Action Coalition

This source provides extensive free provider and patient information, including translations of Vaccine Information Statements into multiple languages. Printed materials are reviewed by CDC for technical accuracy (http://www.immunize.org and http://vaccineinformation.org).

National Network for Immunization Information

This information source is an affiliation of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, AAP, the American Nurses Association, the AAFP, the National Association of Pediatric Nurse Practitioners, the American College of Obstetricians and Gynecologists and the University of Texas Medical Branch. This source seeks to provide the public, health professionals, policy makers, and the media with up-to-date, scientifically valid information (http://www.immunizationinfo.org).

Vaccine Education Center

Located at the Children's Hospital of Philadelphia, this source provides patient and provider information (http://www.vaccine.chop.edu).

Institute for Vaccine Safety

Located at Johns Hopkins University School of Public Health, this source provides information about vaccine safety concerns and objective and timely information to physicians and health-care providers and parents (http://www.vaccinesafety.edu).

Group on Immunization Education of the Society of Teachers of Family Medicine

This organization provides information for clinicians, including the free personal digital assistant software called "Shots" which includes the childhood and adult schedule for Palm OS and for Windows handhelds (http://www.immunizationed.org).

State and Local Health Departments

State and local health departments provide technical advice through hotlines, electronic mail, and Internet sites, including printed information regarding vaccines and immunization schedules, posters, and other educational materials.

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Abbreviations Used in This Publication

AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
ACIP	Advisory Committee on Immunization Practices
DT	pediatric diphtheria-tetanus toxoid
DTaP	pediatric diphtheria and tetanus toxoids and acellular pertussis vaccine
DTP	pediatric diphtheria and tetanus toxoids and whole-cell pertussis vaccine
EIA/ELISA	enzyme immunoassay
FDA	Food and Drug Administration
GBS	Guillain-Barré syndrome
HBIG	hepatitis B immune globulin
HbOC	Haemophilus influenzae type b-diphtheria CRM197 (CRM, cross-reactive material) protein conjugate
HBsAg	hepatitis B surface antigen
Hib	*Haemophilus influenzae* type b
HIV	human immunodeficiency virus
HPV	human papillomavirus
HSCT	hematopoietic stem cell transplant
IgG	immunoglobulin G
IGIV	intravenous immune globulin
IPV	inactivated poliovirus vaccine
JI	jet injector
MCV4	meningococcal conjugate vaccine
MMR	measles, mumps, rubella vaccine
MMRV	measles-mumps-rubella-varicella vaccine
MPSV	meningococcal polysaccharide vaccine
OPV	oral poliovirus vaccine
OSHA	Occupational Safety and Health Administration
PCV	pneumococcal conjugate vaccine
PPD	purified protein derivative
PRP-OMP	Haemophilus influenzae type b-polyribosylribitol phosphate-meningococcal outer membrane protein conjugate
PPV	pneumococcal polysaccharide vaccine
RV	pentavalent rotavirus vaccine
Td	adult tetanus-diphtheria toxoid
Tdap	Tetanus reduced diphtheria acellular pertussis vaccine for adolescents and adults
TST	tuberculin skin test
VAERS	Vaccine Adverse Event Reporting System
VAPP	vaccine-associated paralytic poliomyelitis
VICP	Vaccine Injury Compensation Program
VIS	Vaccine Information Statement

Definitions Used in This Report

Adverse event. An untoward event that occurs after a vaccination that might be caused by the vaccine product or vaccination process. It includes events that are 1) vaccine-induced: caused by the intrinsic characteristic of the vaccine preparation and the individual response of the vaccinee; these events would not have occurred without vaccination (e.g., vaccine-associated paralytic poliomyelitis); 2) vaccine-potentiated: the events would have occurred anyway, but were precipitated by the vaccination (e.g., first febrile seizure in a predisposed child); 3) programmatic error: the event was caused by technical errors in vaccine preparation, handling, or administration; 4) coincidental: the event was associated temporally with vaccination by chance or caused by underlying illness. Special studies are needed to determine if an adverse event is a reaction to the vaccine or the result of another cause (**Sources:** Chen RT. Special methodological issues in pharmacoepidemiology studies of vaccine safety. In: Strom BL, ed. Pharmacoepidemiology. 3rd ed. Sussex, England: John Wiley & Sons; 2000:707–32; and Fenichel GM, Lane DA, Livengood JR, Horwitz SJ, Menkes JH, Schwartz JF. Adverse events following

immunization: assessing probability of causation. Pediatr Neurol 1989;5:287–90).

Adverse reaction. An undesirable medical condition that has been demonstrated to be caused by a vaccine. Evidence for the causal relation is usually obtained through randomized clinical trials, controlled epidemiologic studies, isolation of the vaccine strain from the pathogenic site, or recurrence of the condition with repeated vaccination (i.e., rechallenge); synonyms include side effect and adverse effect.

Immunobiologic. Antigenic substances (e.g., vaccines and toxoids) or antibody-containing preparations (e.g., globulins and antitoxins) from human or animal donors. These products are used for active or passive immunization or therapy. The following are examples of immunobiologics:

Vaccine. A suspension of live (usually attenuated) or inactivated microorganisms (e.g., bacteria or viruses) or fractions thereof administered to induce immunity and prevent infectious disease or its sequelae. Some vaccines contain highly defined antigens (e.g., the polysaccharide of *Haemophilus influenzae* type b or the surface antigen of hepatitis B); others have antigens that are complex or incompletely defined (e.g., *Bordetella pertussis* antigens or live-attenuated viruses).

Toxoid. A modified bacterial toxin that has been made nontoxic, but retains the ability to stimulate the formation of antibodies to the toxin.

Immune globulin. A sterile solution containing antibodies, which are usually obtained from human blood. It is obtained by cold ethanol fractionation of large pools of blood plasma and contains 15%–18% protein. Intended for intramuscular administration, immune globulin is primarily indicated for routine maintenance of immunity among certain immunodeficient persons and for passive protection against measles and hepatitis A.

Intravenous immune globulin. A product derived from blood plasma from a donor pool similar to the immune globulin pool, but prepared so that it is suitable for intravenous use. Intravenous immune globulin is used primarily for replacement therapy in primary antibody-deficiency disorders, for treatment of Kawasaki disease, immune thrombocytopenic purpura, hypogammaglobulinemia in chronic lymphocytic leukemia, and certain cases of human immunodeficiency virus infection (Table 4).

Hyperimmune globulin (specific). Special preparations obtained from blood plasma from donor pools preselected for a high antibody content against a specific antigen (e.g., hepatitis B immune globulin, varicella-zoster immune globulin, rabies immune globulin, tetanus immune globulin, vaccinia immune globulin, cytomegalovirus immune globulin, botulism immune globulin).

Monoclonal antibody. An antibody product prepared from a single lymphocyte clone, which contains only antibody against a single antigen.

Antitoxin. A solution of antibodies against a toxin. Antitoxin can be derived from either human (e.g., tetanus immune globulin) or animal (usually equine) sources (e.g., diphtheria and botulism antitoxin). Antitoxins are used to confer passive immunity and for treatment.

Vaccination and immunization. The terms vaccine and vaccination are derived from vacca, the Latin term for cow. Vaccine was the term used by Edward Jenner to describe material used (i.e., cowpox virus) to produce immunity to smallpox. The term vaccination was used by Louis Pasteur in the 19th century to include the physical act of administering any vaccine or toxoid. Immunization is a more inclusive term, denoting the process of inducing or providing immunity by administering an immunobiologic. Immunization can be active or passive. Active immunization is the production of antibody or other immune responses through administration of a vaccine or toxoid. Passive immunization means the provision of temporary immunity by the administration of preformed antibodies. Although persons often use the terms vaccination and immunization interchangeably in reference to active immunization, the terms are not synonymous because the administration of an immunobiologic cannot be equated automatically with development of adequate immunity.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

Goals and Objectives

This *MMWR* provides general guidelines on immunization. The goal of this report is improve vaccination practices in the United States. Upon completion of this educational activity, the reader should be able to 1) identity valid contraindications for commonly used vaccines, 2) identify the minimum spacing between doses for vaccines routinely used in the United States, 3) describe recommended methods for administration of vaccines, and 4) identify evidence-based interventions shown to improve vaccination rates among children.

To receive continuing education credit, please answer all of the following questions.

1. If a second dose of a live virus vaccine is determined to be invalid, when should another dose be administered?
- A. As soon as possible.
- B. 28 days after the most recent valid dose.
- C. 28 days from the invalid dose or a minimum interval from the invalid dose, whichever is longer.
- D. A minimum interval from the most recent valid dose.
- E. Never. You must start the series over.

2. Which of the following is a permanent contraindication for all vaccines?
- A. Progressive neurologic disorder.
- B. Pregnancy.
- C. Severe allergic reaction to a previous dose of vaccine.
- D. Family history of asthma.
- E. Fever.

3. Which factor is an important criterion for needle length for a subcutaneous injection?
- A. Body mass.
- B. Site of injection.
- C. Sex.
- D. Age.
- E. None of the above.

4. Which test is NOT considered a suitable test to assess the level of altered immunocompetence?
- A. Immunoglobulin subclasses.
- B. Pertussis titers.
- C. Lymphocyte proliferation assays.
- D. T-cell counts.
- E. Antibody response to adult tetanus-diphtheria toxoid antigen.

5. The combination measles-mumps-rubella-varicella (MMRV) vaccine...
- A. is an inactivated vaccine.
- B. is contraindicated in pregnancy.
- C. is recommended if a person has a contraindication to one of the single-antigen vaccines (like monovalent varicella vaccine).
- D. must be refrigerated.
- E. requires more injections than measles-mumps-rubella (MMR) vaccine.

6. Which of the following strategy is not specifically recommended to improve vaccination coverage in children?
- A. Provision of vaccines at child care centers.
- B. Enhancing access to vaccines at schools.
- C. Laws requiring vaccines for school entry.
- D. Enhancing access to vaccines through the Women, Infants, and Children program.
- E. Reminder and recall systems.

7. The minimum intervals for vaccines should be used...
- A. to schedule a patient's next visit.
- B. to avoid simultaneous administration of vaccines.
- C. to catch-up children that are behind on vaccine doses.
- D. to avoid giving two injections at the same site.
- E. by vaccine registries to construct recall messages for providers.

8. Which is an acceptable way of alleviating the pain and discomfort of children as part of the vaccination process?
- A. Combining acetaminophen with topical EMLA therapy.
- B. Distraction methods (e.g., blowing away the pain).
- C. Telling children that vaccination doesn't hurt.
- D. Assurance that most adverse reactions are mild.
- E. None of the above.

9. Which of the following is a contraindication to MMR vaccine?
- A. Positive tuberculin skin test (TST) skin test.
- B. Simultaneous testing using TST.
- C. Allergy to eggs.
- D. Pregnancy.
- E. A household contact with altered immunocompetence.

10. If a storage unit has been found to be maintained at temperatures outside the recommended range for the vaccines contained within, which of the following would be an appropriate action?
- A. Discard all vaccines contained in the unit.
- B. Continue using the vaccine after it has been transferred to another storage unit.
- C. Mark the vaccine "Do not use" until more can be determined about the usability of the vaccine.
- D. Shorten the expiration date by 1 month.
- E. Recalibrate the thermometer.

11. Which best describes your professional activities?
- A. Physician.
- B. Nurse.
- C. Health educator.
- D. Office staff.
- E. Other.

12. I plan to use these recommendations as the basis for …(*Indicate all that apply.*)
- A. health education materials.
- B. insurance reimbursement policies.
- C. local practice guidelines.
- D. public policy.
- E. other.

13. Overall, the length of the journal report was…
- A. much too long.
- B. a little too long.
- C. just right.
- D. a little too short.
- E. much too short.

14. After reading this report, I am confident I can identify valid contraindications for commonly used vaccines.
- A. Strongly agree.
- B. Agree.
- C. Undecided.
- D. Disagree.
- E. Strongly disagree.

15. After reading this report, I am confident I can identify the minimum spacing between doses for vaccines routinely used in the United States.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

16. After reading this report, I am confident I can describe recommended methods for administration of vaccines.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

17. After reading this report, I am confident I can identify evidence-based interventions shown to improve vaccination rates among children.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

18. The learning outcomes (objectives) were relevant to the goals of this report.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

19. The instructional strategies used in this report (text, tables, and figures) helped me learn the material.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

20. The content was appropriate given the stated objectives of the report.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

21. The content expert(s) demonstrated expertise in the subject matter.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree

22. Overall, the quality of the journal report was excellent.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

(Continued on pg CE-4)

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December 1, 2006/Vol. 55/No. RR-15

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5. [ ]A [ ]B [ ]C [ ]D [ ]E	19. [ ]A [ ]B [ ]C [ ]D [ ]E		
6. [ ]A [ ]B [ ]C [ ]D [ ]E	20. [ ]A [ ]B [ ]C [ ]D [ ]E		
7. [ ]A [ ]B [ ]C [ ]D [ ]E	21. [ ]A [ ]B [ ]C [ ]D [ ]E		
8. [ ]A [ ]B [ ]C [ ]D [ ]E	22. [ ]A [ ]B [ ]C [ ]D [ ]E		
9. [ ]A [ ]B [ ]C [ ]D [ ]E	23. [ ]A [ ]B [ ]C [ ]D [ ]E		
10. [ ]A [ ]B [ ]C [ ]D [ ]E	24. [ ]A [ ]B [ ]C [ ]D [ ]E		
11. [ ]A [ ]B [ ]C [ ]D [ ]E	25. [ ]A [ ]B [ ]C [ ]D [ ]E		
12. [ ]A [ ]B [ ]C [ ]D [ ]E	26. [ ]A [ ]B		
13. [ ]A [ ]B [ ]C [ ]D [ ]E	27. [ ]A [ ]B [ ]C [ ]D [ ]E [ ]F		
14. [ ]A [ ]B [ ]C [ ]D [ ]E			

Signature ***Date I Completed Exam***

23. These recommendations will improve the quality of my practice.

A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

24. The availability of continuing education credit influenced my decision to read this report.

A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

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A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

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Correct answers for questions 1–10: 1. C; 2. C; 3. E; 4. B; 5. B; 6. A; 7. C; 8. B; 9. D; 10. C.

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Recommendations and Reports

MORBIDITY AND MORTALITY WEEKLY REPORT

Immunization of Health-Care Workers

Recommendations of the Advisory Committee on Immunization Practices (ACIP) and the Hospital Infection Control Practices Advisory Committee (HICPAC)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control and Prevention (CDC)
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Immunization of Health-Care Workers:

Recommendations of the Advisory Committee on Immunization Practices (ACIP) and the Hospital Infection Control Practices Advisory Committee (HICPAC)

Summary

This report summarizes recommendations of the Advisory Committee on Immunization Practices (ACIP) concerning the use of certain immunizing agents in health-care workers (HCWs) in the United States. It was prepared in consultation with the Hospital Infection Control Practices Advisory Committee (HICPAC) and is consistent with current HICPAC guidelines for infection control in health-care personnel. These recommendations can assist hospital administrators, infection control practitioners, employee health physicians, and HCWs in optimizing infection prevention and control programs. Background information for each vaccine-preventable disease and specific recommendations for use of each vaccine are presented. The diseases are grouped into three categories: a) those for which active immunization is strongly recommended because of special risks for HCWs; b) those for which immunoprophylaxis is or may be indicated in certain circumstances; and c) those for which protection of all adults is recommended. This report reflects current ACIP recommendations at the time of publication. ACIP statements on individual vaccines and disease updates in MMWR *should be consulted for more details regarding the epidemiology of the diseases, immunization schedules, vaccine doses, and the safety and efficacy of the vaccines.*

INTRODUCTION

Because of their contact with patients or infective material from patients, many health-care workers (HCWs)(e.g., physicians, nurses, emergency medical personnel, dental professionals and students, medical and nursing students, laboratory technicians, hospital volunteers, and administrative staff) are at risk for exposure to and possible transmission of vaccine-preventable diseases. Maintenance of immunity is therefore an essential part of prevention and infection control programs for HCWs. Optimal use of immunizing agents safeguards the health of workers and protects patients from becoming infected through exposure to infected workers (Table 1) (*1–15*). Consistent immunization programs could substantially reduce both the number of susceptible HCWs in hospitals and health departments and the attendant risks for transmission of vaccine-preventable diseases to other workers and patients (*16*). In addition to HCWs in hospitals and health departments, these recommendations apply to those in private physicians' offices, nursing homes, schools, and laboratories, and to first responders.

Any medical facility or health department that provides direct patient care is encouraged to formulate a comprehensive immunization policy for all HCWs. The American Hospital Association has endorsed the concept of immunization programs

TABLE 1. Recommendations for immunization practices and use of immunobiologics applicable to disease prevention among health-care workers — Advisory Committee on Immunization Practices (ACIP) statements published as of September 1, 1997

Subject	MMWR Publication
General recommendations on immunization	1994;43(No.RR-1):1-39
Adult immunization	1991;40(No.RR-12):1-94
Altered immunocompetence	1993;42(No.RR-4):1-18
Adverse reactions, contraindications, and precautions	1996;45(No.RR-12):1-35
Bacille Calmette-Guérin vaccine	1996;45(No.RR-4):1-18
Diphtheria, tetanus, and pertussis	1991;40(No.RR-10):1-28 1997;46(No. RR-7)
Hepatitis B	1991;40(No.RR-13):1-25
Hepatitis A	1996;45(No.RR-15):1-30
Influenza*	1997;46(No.RR-9):1-25
Japanese encephalitis	1993;42(No.RR-1):1-15
Measles	1989;38(No.S9):1-18
Measles, mumps, rubella (MMR)	1998;47 (in press)
Meningococcal disease and outbreaks	1997;46(No.RR-5):1-21
Mumps (MMR in press, see Measles above)	1989;38:388–92, 397–400
Pertussis, acellular (see also Diphtheria above) (supplementary statements)	1992;41(No.RR-1):1-10 1992;41(No.RR-15):1-5 1997;46(No.RR-7):1-25
Pneumococcal	1997;46(No.RR-8):1-24
Poliomyelitis	1997;46(No.RR-3):1-25
Rabies	1991;40(No.RR-3):1-19
Rubella (MMR in press, see Measles above)	1990;39(No.RR-15):1-18
Typhoid	1994;43(No.RR-14):1-7
Vaccinia (smallpox)	1991;40(No.RR-14):1-10
Varicella	1996;45(No.RR-11):1-36

*Each year influenza vaccine recommendations are reviewed and amended to reflect updated information concerning influenza activity in the United States for the preceding influenza season and to provide information on the vaccine available for the upcoming influenza season. These recommendations are published annually in the MMWR, usually during May or June.

for both hospital personnel and patients (*17*). The following recommendations concerning vaccines of importance to HCWs should be considered during policy development (Table 2).

BACKGROUND

Diseases for Which Immunization Is Strongly Recommended

On the basis of documented nosocomial transmission, HCWs are considered to be at significant risk for acquiring or transmitting hepatitis B, influenza, measles, mumps, rubella, and varicella. All of these diseases are vaccine-preventable.

Hepatitis B

Hepatitis B virus (HBV) infection is the major infectious hazard for health-care personnel. During 1993, an estimated 1,450 workers became infected through exposure to blood and serum-derived body fluids, a 90% decrease from the number estimated to have been thus infected during 1985 (*18–20*). Data indicate that 5%–10% of HBV-infected workers become chronically infected. Persons with chronic HBV infection are at risk for chronic liver disease (i.e., chronic active hepatitis, cirrhosis, and primary hepatocellular carcinoma) and are potentially infectious throughout their lifetimes. An estimated 100–200 health-care personnel have died annually during the past decade because of the chronic consequences of HBV infection (CDC, unpublished data).

The risk for acquiring HBV infection from occupational exposures is dependent on the frequency of percutaneous and permucosal exposures to blood or body fluids containing blood (*21–25*). Depending on the tasks he or she performs, any health-care or public safety worker may be at high risk for HBV exposure. Workers performing tasks involving exposure to blood or blood-contaminated body fluids should be vaccinated. For public safety workers whose exposure to blood is infrequent, timely postexposure prophylaxis may be considered, rather than routine preexposure vaccination.

In 1987, the Departments of Labor and Health and Human Services issued a Joint Advisory Notice regarding protection of employees against workplace exposure to HBV and human immunodeficiency virus (HIV), and began the process of rulemaking to regulate such exposures (*26*). The Federal Standard issued in December, 1991 under the Occupational Safety and Health Act mandates that hepatitis B vaccine be made available at the employer's expense to all health-care personnel who are occupationally exposed to blood or other potentially infectious materials (*27*). Occupational exposure is defined as "...reasonably anticipated skin, eye, mucous membrane, or parenteral contact with blood or other potentially infectious materials that may result from the performance of an employee's duties (*27*)." The Occupational Safety and Health Administration (OSHA) follows current ACIP recommendations for its immunization practices requirements (e.g., preexposure and postexposure antibody testing). These regulations have accelerated and broadened the use of hepatitis B vaccine in HCWs and have ensured maximal efforts to prevent this occupational disease (*23*).

Prevaccination serologic screening for prior infection is not indicated for persons being vaccinated because of occupational risk. Postvaccination testing for antibody to hepatitis B surface antigen (anti-HBs) response is indicated for HCWs who have blood or patient contact and are at ongoing risk for injuries with sharp instruments or needlesticks (e.g., physicians, nurses, dentists, phlebotomists, medical technicians and students of these professions). Knowledge of antibody response aids in determining appropriate postexposure prophylaxis.

TABLE 2. Immunizing agents and immunization schedules for health-care workers (HCWs)*

Generic name	Primary schedule and booster(s)	Indications	Major precautions and contraindications	Special considerations
IMMUNIZING AGENTS STRONGLY RECOMMENDED FOR HEALTH-CARE WORKERS				
Hepatitis B (HB) recombinant vaccine	Two doses IM 4 weeks apart; third dose 5 months after second; booster doses not necessary.	**Preexposure:** HCWs at risk for exposure to blood or body fluids. **Postexposure:** See Table 3.	On the basis of limited data, no risk of adverse effects to developing fetuses is apparent. Pregnancy should *not* be considered a contraindication to vaccination of women. Previous anaphylactic reaction to common baker's yeast is a contraindication to vaccination.	The vaccine produces neither therapeutic nor adverse effects on HBV-infected persons. Prevaccination serologic screening is not indicated for persons being vaccinated because of occupational risk. HCWs who have contact with patients or blood should be tested 1–2 months after vaccination to determine serologic response.
Hepatitis B immune globulin (HBIG)	0.06 mL/kg IM as soon as possible after exposure. A second dose of HBIG should be administered 1 month later if the HB vaccine series has not been started.	**Postexposure** prophylaxis (Table 3): For persons exposed to blood or body fluids containing HBsAg and who are not immune to HBV infection — 0.06 mL/kg IM as soon as possible (but no later than 7 days after exposure).		
Influenza vaccine (inactivated whole-virus and split-virus vaccines)	Annual vaccination with current vaccine. Administered IM.	HCWs who have contact with patients at high risk for influenza or its complications; HCWs who work in chronic care facilities; HCWs with high-risk medical conditions or who are aged ≥65 years.	History of anaphylactic hypersensitivity to egg ingestion.	No evidence exists of risk to mother or fetus when the vaccine is administered to a pregnant woman with an underlying high-risk condition. Influenza vaccination is recommended during second and third trimesters of pregnancy because of increased risk for hospitalization.

Measles live-virus vaccine	One dose SC; second dose at least 1 month later.	HCWs[†] born during or after 1957 who do not have documentation of having received 2 doses of live vaccine on of after the first birthday **or** a history of physician-diagnosed measles or serologic evidence of immunity. Vaccination should be considered for all HCWs who lack proof of immunity, including those born before 1957.	Pregnancy; immunocompromised persons[§], including HIV-infected persons who have evidence of severe immunosuppression; anaphylaxis after gelatin ingestion or administration of neomycin; recent administration of immune globulin.	MMR is the vaccine of choice if recipients are likely to be susceptible to rubella and/or mumps as well as to measles. Persons vaccinated during 1963–1967 with a killed measles vaccine alone, killed vaccine followed by live vaccine, or with a vaccine of unknown type should be revaccinated with 2 doses of live measles virus vaccine.
Mumps live-virus vaccine	One dose SC; no booster.	HCWs[†] believed to be susceptible can be vaccinated. Adults born before 1957 can be considered immune.	Pregnancy; immunocompromised persons[§]; history of anaphylactic reaction after gelatin ingestion or administration of neomycin.	MMR is the vaccine of choice if recipients are likely to be susceptible to measles and rubella as well as to mumps.

[*] Persons who provide health care to patients or work in institutions that provide patient care, e.g., physicians, nurses, emergency medical personnel, dental professionals and students, medical and nursing students, laboratory technicians, hospital volunteers, and administrative and support staff in health-care institutions

[†] All HCWs (i.e., medical or nonmedical, paid or volunteer, full time or part time, student or non-student, with or without patient-care responsibilities) who work in health-care institutions (e.g., inpatient and outpatient, public and private) should be immune to measles, rubella, and varicella.

[§] Persons immunocompromised because of immune deficiency diseases, HIV infection, leukemia, lymphoma or generalized malignancy or immunosuppressed as a result of therapy with corticosteroids, alkylating drugs, antimetabolites, or radiation.

Abbreviations: IM = intramuscular; HBV = hepatitis B virus; HBsAg = hepatitis B surface antigen; SC = subcutaneous; HIV = human immunodeficiency virus; MMR = measles, mumps, rubella vaccine.

TABLE 2. Immunizing agents and immunization schedules for health-care workers (HCWs)* — Continued

Generic name	Primary schedule and booster(s)	Indications	Major precautions and contraindications	Special considerations
Rubella live-virus vaccine	One dose SC; no booster	Indicated for HCWs†, both men and women, who do not have documentation of having received live vaccine on or after their first birthday **or** laboratory evidence of immunity. Adults born before 1957, **except women who can become pregnant,** can be considered immune.	Pregnancy; immunocompromised persons†; history of anaphylactic reaction after administration of neomycin.	The risk for rubella vaccine-associated malformations in the offspring of women pregnant when vaccinated or who become pregnant within 3 months after vaccination is negligible. Such women should be counseled regarding the theoretical basis of concern for the fetus. MMR is the vaccine of choice if recipients are likely to be susceptible to measles or mumps, as well as to rubella.
Varicella zoster live-virus vaccine	Two 0.5 mL doses SC 4-8 weeks apart if ≥13 years of age.	Indicated for HCWs† who do not have either a reliable history of varicella or serologic evidence of immunity.	Pregnancy, immunocompromised persons§, history of anaphylactic reaction following receipt of neomycin or gelatin. Avoid salicylate use for 6 weeks after vaccination.	Vaccine is available from the manufacturer for certain patients with acute lymphocytic leukemia (ALL) in remission. Because 71%-93% of persons without a history of varicella are immune, serologic testing before vaccination is likely to be cost-effective.
Varicella-zoster immune globulin (VZIG)	Persons <50 kg: 125 u/10 kg IM; persons ≥50 kg: 625 u¶.	Persons known or likely to be susceptible (particularly those at high risk for complications, e.g., pregnant women) who have close and prolonged exposure to a contact case or to an infectious hospital staff worker or patient.		Serologic testing may help in assessing whether to administer VZIG. If use of VZIG prevents varicella disease, patient should be vaccinated subsequently.

BCG VACCINATION				
Bacille Calmette Guérin(BCG) Vaccine (Tuberculosis)	One percutaneous dose of 0.3 mL; no booster dose recommended.	Should be considered only for HCWs in areas where multi-drug tuberculosis is prevalent, a strong likelihood of infection exists, and where comprehensive infection control precautions have failed to prevent TB transmission to HCWs.	Should not be administered to immunocompromised persons,[§] pregnant women.	In the United States tuberculosis-control efforts are directed towards early identification, treatment of cases, and preventive therapy with isoniazid.

OTHER IMMUNOBIOLOGICS THAT ARE OR MAY BE INDICATED FOR HEALTH-CARE WORKERS

Generic name	Primary schedule and booster(s)	Indications	Major precautions and contraindications	Special considerations
Immune globulin (Hepatitis A)	**Postexposure**-One IM dose of 0.02 mL/kg administered ≤2 weeks after exposure.	Indicated for HCWs exposed to feces of infectious patients.	Contraindicated in persons with IgA deficiency; do not administer within 2 weeks after MMR vaccine, or 3 weeks after varicella vaccine. Delay administration of MMR vaccine for ≥3 months and varicella vaccine ≥5 months after administration of IG.	Administer in large muscle mass (deltoid, gluteal).

[*] Persons who provide health care to patients or work in institutions that provide patient care, e.g., physicians, nurses, emergency medical personnel, dental professionals and students, medical and nursing students, laboratory technicians, hospital volunteers, and administrative and support staff in health-care institutions.

[†] All HCWs (i.e., medical or nonmedical, paid or volunteer, full-time or part-time, student or nonstudent, with or without patient-care responsibilities) who work in health-care institutions (i.e., inpatient and outpatient, public and private) should be immune to measles, rubella, and varicella.

[§] Persons immunocompromised because of immune deficiency diseases, HIV infection (who should primarily not receive BCG, OPV, and yellow fever vaccines), leukemia, lymphoma or generalized malignancy or immunosuppressed as a result of therapy with corticosteroids, alkylating drugs, antimetabolites, or radiation.

¶ Some experts recommend 125 u/10 kg regardless of total body weight.

Abbreviations: IM = intramuscular; HCW = health-care worker; TB = tuberculosis; MMR = measles, mumps, rubella vaccine; HAV = hepatitis A virus; SC = subcutaneous; IgA = immune globulin A.

TABLE 2. Immunizing agents and immunization schedules for health-care workers (HCWs)* — Continued

Generic name	Primary schedule and booster(s)	Indications	Major precautions and contraindications	Special considerations
Hepatitis A vaccine	Two doses of vaccine either 6-12 months apart (HAVRIX®), or 6 months apart (VAQTA®).	Not routinely indicated for HCWs in the United States. Persons who work with HAV-infected primates or with HAV in a research laboratory setting should be vaccinated.	History of anaphylactic hypersensitivity to alum or, for HAVRIX®, the preservative 2-phenoxyethanol. The safety of the vaccine in pregnant women has not been determined; the risk associated with vaccination should be weighed against the risk for hepatitis A in women who may be at high risk for exposure to HAV.	
Meningococcal polysaccharide vaccine (tetravalent A, C, W135, and Y)	One dose in volume and by route specified by manufacturer; need for boosters unknown.	Not routinely indicated for HCWs in the United States.	The safety of the vaccine in pregnant women has not been evaluated; it should not be administered during pregnancy unless the risk for infection is high.	
Typhoid vaccine, IM, SC, and oral	*IM vaccine:* One 0.5 mL dose, booster 0.5 mL every 2 years. *SC vaccine:* two 0.5 mL doses, ≥4 weeks apart, booster 0.5 mL SC or 0.1 ID every 3 years if exposure continues. *Oral vaccine:* Four doses on alternate days. The manufacturer recommends revaccination with the entire four-dose series every 5 years.	Workers in microbiology laboratories who frequently work with *Salmonella typhi.*	Severe local or systemic reaction to a previous dose. Ty21a (oral) vaccine should not be administered to immunocompromised persons† or to persons receiving antimicrobial agents.	Vaccination should not be considered an alternative to the use of proper procedures when handling specimens and cultures in the laboratory.

Vaccinia vaccine (smallpox)	One dose administered with a bifurcated needle; boosters administered every 10 years.	Laboratory workers who directly handle cultures with vaccinia, recombinant vaccinia viruses, or orthopox viruses that infect humans.	The vaccine is contraindicated in pregnancy, in persons with eczema or a history of eczema, and in immunocompromised persons[†] and their household contacts.	Vaccination may be considered for HCWs who have direct contact with contaminated dressings or other infectious material from volunteers in clinical studies involving recombinant vaccinia virus.
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Tetanus and diphtheria (toxoids [Td])	Two IM doses 4 weeks apart; third dose 6-12 months after second dose; booster every 10 years.	All adults.	Except in the first trimester, pregnancy is not a precaution. History of a neurologic reaction or immediate hypersensitivity reaction after a previous dose. History of severe local (Arthus-type) reaction after a previous dose. Such persons should not receive further routine or emergency doses of Td for 10 years.	Tetanus prophylaxis in wound management[§].
Pneumococcal polysaccharide vaccine (23 valent).	One dose, 0.5 mL, IM or SC; revaccination recommended for those at highest risk ≥5 years after the first dose.	Adults who are at increased risk of pneumococcal disease and its complications because of underlying health conditions; older adults, especially those age ≥65 who are healthy.	The safety of vaccine in pregnant women has not been evaluated; it should not be administered during pregnancy unless the risk for infection is high. Previous recipients of any type of pneumococcal polysaccharide vaccine who are at highest risk for fatal infection or antibody loss may be revaccinated ≥5 years after the first dose.	

[*] Persons who provide health care to patients or work in institutions that provide patient care, e.g., physicians, nurses, emergency medical personnel, dental professionals and students, medical and nursing students, laboratory technicians, hospital volunteers, and administrative and support staff in health-care institutions.

[†] Persons immunocompromised because of immune deficiency diseases, HIV infection, leukemia, lymphoma or generalized malignancy or immunosuppressed as a result of therapy with corticosteroids, alkylating drugs, antimetabolites, or radiation.

[§] See (15) CDC. Update on adult immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1991:40(No. RR-12):1–94.

Abbreviations: IM = intramuscular; ID = intradermal; SC = subcutaneous.

Vaccine-induced antibodies to HBV decline gradually over time, and ≤60% of persons who initially respond to vaccination will lose detectable antibodies over 12 years (*28* ; CDC, unpublished data). Studies among adults have demonstrated that, despite declining serum levels of antibody, vaccine-induced immunity continues to prevent clinical disease or detectable viremic HBV infection (*29*). Therefore, booster doses are not considered necessary (*1*). Periodic serologic testing to monitor antibody concentrations after completion of the three-dose series is not recommended. The possible need for booster doses will be assessed as additional data become available.

Asymptomatic HBV infections have been detected in vaccinated persons by means of serologic testing for antibody to hepatitis B core antigen (anti-HBc) (*1*). However, these infections also provide lasting immunity and are not associated with HBV-related chronic liver disease.

Influenza

During community influenza outbreaks, admitting patients infected with influenza to hospitals has led to nosocomial transmission of the disease (*30,31*), including transmission from staff to patients (*32*). Transmission of influenza among medical staff causes absenteeism and considerable disruption of health care (*33–36* ; CDC, unpublished data). In addition, influenza outbreaks have caused morbidity and mortality in nursing homes (*36–41*). In a recent study of long-term care facilities with uniformly high patient influenza vaccination levels, patients in facilities in which >60% of the staff had been vaccinated against influenza experienced less influenza-related mortality and illness, compared with patients in facilities with no influenza-vaccinated staff (*42*).

Measles, Mumps, and Rubella

Measles. Nosocomial measles transmission has been documented in the offices of private physicians, in emergency rooms, and on hospital wards (*43–49*). Although only 3.5% of all cases of measles reported during 1985–1989 occurred in medical settings, the risk for measles infection in medical personnel is estimated to be thirteenfold that for the general population (*45,49–52*). During 1990–1991, 1,788 of 37,429 (4.8%) measles cases were reported to have been acquired in medical settings. Of these, 668 (37.4%) occurred among HCWs, 561 (84%) of whom were unvaccinated; 187 (28%) of these HCWs were hospitalized with measles and three died (CDC, unpublished data). Of the 3,659 measles cases reported during 1992–1995, the setting of transmission was known for 2,765; 385 (13.9%) of these cases occurred in medical settings (CDC, unpublished data).

Although birth before 1957 is generally considered acceptable evidence of measles immunity, serologic studies of hospital workers indicate that 5%–9% of those born before 1957 are not immune to measles (*53,54*). During 1985–1992, 27% of all measles cases among HCWs occurred in persons born before 1957 (CDC, unpublished data).

Mumps. In recent years, a substantial proportion of reported mumps has occurred among unvaccinated adolescents and young adults on college campuses and in the workplace (*55–58*). Outbreaks of mumps in highly vaccinated populations have been attributed to primary vaccine failure (*59,60*). During recent years, the overall incidence of mumps has fluctuated only minimally but an increasing proportion of cases has been reported in persons aged ≥15 years (*61*). Mumps transmission in medical set-

tings has been reported nationwide (*62 ,* CDC, unpublished data). Programs to ensure that medical personnel are immune to mumps are prudent and are easily linked with measles and rubella control programs (*5*).

Rubella. Nosocomial rubella outbreaks involving both HCWs and patients have been reported (*63*). Although vaccination has decreased the overall risk for rubella transmission in all age groups in the United States by ≥95%, the potential for transmission in hospital and similar settings persists because 10%–15% of young adults are still susceptible (*6,64–67*). In an ongoing study of rubella vaccination in a health maintenance organization, 7,890 of 92,070 (8.6%) women aged ≥29 years were susceptible to rubella (CDC, unpublished data). Although not as infectious as measles, rubella can be transmitted effectively by both males and females. Transmission can occur whenever many susceptible persons congregate in one place. Aggressive rubella vaccination of susceptible men and women with trivalent measles-mumps-rubella (MMR) vaccine can eliminate rubella (as well as measles) transmission (*68*).

Persons born before 1957 generally are considered to be immune to rubella. However, findings of seroepidemiologic studies indicate that about 6% of HCWs (including persons born in 1957 or earlier) do not have detectable rubella antibody (CDC, unpublished data).

Varicella

Nosocomial transmission of varicella zoster virus (VZV) is well recognized (*69–80*). Sources for nosocomial exposure of patients and staff have included patients, hospital staff, and visitors (e.g., the children of hospital employees) who are infected with either varicella or zoster. In hospitals, airborne transmission of VZV from persons who had varicella or zoster to susceptible persons who had no direct contact with the index case-patient has occurred (*81–85*). Although all susceptible hospitalized adults are at risk for severe varicella disease and complications, certain patients are at increased risk: pregnant women, premature infants born to susceptible mothers, infants born at <28 weeks' gestation or who weigh ≤1000 grams regardless of maternal immune status, and immunocompromised persons of all ages (including persons who are undergoing immunosuppressive therapy, have malignant disease, or are immunodeficient).

Varicella Control Strategies

Strategies for managing clusters of VZV infections in hospitals include (*16,86–94*):

- isolating patients who have varicella and other susceptible patients who are exposed to VZV;
- controlling air flow;
- using rapid serologic testing to determine susceptibility;
- furloughing exposed susceptible personnel or screening these persons daily for skin lesions, fever, and systemic symptoms; and
- temporarily reassigning varicella-susceptible personnel to locations remote from patient-care areas.

Appropriate isolation of hospitalized patients who have confirmed or suspected VZV infection can reduce the risk for transmission to personnel (*95*).

Identification of the few persons who are susceptible to varicella when they begin employment that involves patient contact is recommended. Only personnel who are immune to varicella should care for patients who have confirmed or suspected varicella or zoster.

A reliable history of chickenpox is a valid measure of VZV immunity. Serologic tests have been used to assess the accuracy of reported histories of chickenpox (*76,80,93,95–97*). Among adults, 97% to 99% of persons with a positive history of varicella are seropositive. In addition, the majority of adults with negative or uncertain histories are seropositive (range: 71%–93%). Persons who do not have a history of varicella or whose history is uncertain can be considered susceptible, or tested serologically to determine their immune status. In health-care institutions, serologic screening of personnel who have a negative or uncertain history of varicella is likely to be cost effective (*8*).

If susceptible HCWs are exposed to varicella, they are potentially infective 10–21 days after exposure. They must often be furloughed during this period, usually at substantial cost. Persons in whom varicella develops are infective until all lesions dry and crust (*16,35,96–98*) (see Other Considerations in Vaccination of Health-Care Workers—Work Restrictions for Susceptible Workers After Exposure).

Administration of varicella zoster immune globulin (VZIG) after exposure can be costly. VZIG does not necessarily prevent varicella, and may prolong the incubation period by a week or more, thus extending the time during which personnel should not work.

Breakthrough Infection and Transmission of Vaccine Virus to Contacts

Varicella virus vaccine protects approximately 70%–90% of recipients against infection and 95% of recipients against severe disease for at least 7–10 years after vaccination. Significant protection is long-lasting. Breakthrough infections (i.e., cases of varicella) have occurred among vaccinees after exposure to natural varicella virus. Data from all trials in which vaccinees of all ages were actively followed for up to 9 years indicated that varicella developed in 1%–4.4% of vaccinees per year, depending on vaccine lot and time interval since vaccination (Merck and Company, Inc., unpublished data). Unvaccinated persons who contract varicella generally are febrile and have several hundred vesicular lesions. Among vaccinees who developed varicella, in contrast, the median number of skin lesions was <50 and lesions were less apt to be vesicular. Most vaccinated persons who contracted varicella were afebrile, and the duration of illness was shorter (Merck and Company, Inc., unpublished data; *99,100*).

The rate of transmission of disease from vaccinees who contract varicella is low for vaccinated children, but has not been studied in adults. Ten different trials conducted during 1981–1989 involved 2,141 vaccinated children. Breakthrough infections occurred in 78 children during the 1–8 year follow-up period of active surveillance, resulting in secondary cases in 11 of 90 (12.2%) vaccinated siblings. Among both index and secondary case-patients, illness was mild. Transmission to a susceptible mother from a vaccinated child in whom breakthrough disease occurred also has been reported (Merck and Company, Inc., unpublished data; *101*).

Estimates of vaccine efficacy and persistence of antibody in vaccinees are based on research conducted before widespread use of varicella vaccine began to influence the prevalence of natural VZV infection. Thus, the extent to which boosting from exposure to natural virus increases the protection provided by vaccination remains unclear. Whether longer-term immunity may wane as the circulation of natural VZV decreases also is unknown.

Risk for transmission of vaccine virus was assessed in placebo recipients who were siblings of vaccinated children and among healthy siblings of vaccinated leukemic children (*102,103*). The findings of these studies indicate that healthy vaccinated persons have a minimal risk (estimated to be <1%) for transmitting vaccine virus to their contacts. This risk may be increased in vaccinees in whom a varicella-like rash develops after vaccination. Tertiary transmission of vaccine virus to a second healthy sibling of a vaccinated leukemic child also has occurred (*103*).

Several options for managing vaccinated HCWs who may be exposed to varicella are available. Routine serologic testing for varicella immunity after administration of two doses of vaccine is not considered necessary because 99% of persons become seropositive after the second dose. Seroconversion, however, does not always result in full protection against disease. Institutional guidelines are needed for management of exposed vaccinees who do not have detectable antibody and for those who develop clinical varicella. A potentially effective strategy to identify persons who remain at risk for varicella is to test vaccinated persons for serologic evidence of immunity immediately after they are exposed to VZV. Prompt, sensitive, and specific serologic results can be obtained at reasonable cost with a commercially available latex agglutination (LA) test. Many other methods also have been used to detect antibody to VZV (*8*). The LA test, which uses latex particles coated with VZV glycoprotein antigens, can be completed in 15 minutes (*104,105*). Persons with detectable antibody are unlikely to become infected with varicella. Persons who do not have detectable antibody can be retested in 5–6 days. If an anamnestic response is present, these persons are unlikely to contract the disease. HCWs who do not have antibody when retested may be furloughed. Alternatively, the clinical status of these persons may be monitored daily and they can be furloughed at the onset of manifestations of varicella.

More information is needed concerning risk for transmission of vaccine virus from vaccinees with and without varicella-like rash after vaccination. The risk appears to be minimal, and the benefits of vaccinating susceptible HCWs outweigh this potential risk. As a safeguard, institutions may wish to consider precautions for personnel in whom a rash develops after vaccination and for other vaccinated personnel who will have contact with susceptible persons at high risk for serious complications.

Vaccination should be considered for unvaccinated HCWs who lack documented immunity if they are exposed to varicella. However, because the effectiveness of postexposure vaccination is unknown, persons vaccinated after an exposure should be managed in the manner recommended for unvaccinated persons.

Tuberculosis and Bacille-Calmette-Guérin Vaccination

In the United States, Bacille Calmette-Guérin (BCG) vaccine has not been recommended for general use because the population risk for infection with *Mycobacterium tuberculosis* (TB) is low and the protective efficacy of BCG vaccine uncertain. The im-

mune response to BCG vaccine also interferes with use of the tuberculin skin test to detect *M. tuberculosis* infection (*7*). TB prevention and control efforts are focused on interrupting transmission from patients who have active infectious TB, skin testing those at high risk for TB, and administering preventive therapy when appropriate. However, in certain situations, BCG vaccination may contribute to the prevention and control of TB when other strategies are inadequate.

Control of TB

The fundamental strategies for the prevention and control of TB include:

- Early detection and effective treatment of patients with active communicable TB (*106*).
- Preventive therapy for infected persons. Identifying and treating persons who are infected with *M. tuberculosis* can prevent the progression of latent infection to active infectious disease (*107*).
- Prevention of institutional transmission. The transmission of TB is a recognized risk in health-care settings and is of particular concern in settings where HIV-infected persons work, volunteer, visit, or receive care (*108*). Effective TB infection-control programs should be implemented in health-care facilities and other institutional settings, (e.g., shelters for homeless persons and correctional facilities) (*16,109,110*).

Role of BCG Vaccination in Prevention of TB Among HCWs

In a few geographic areas of the United States, increased risks for TB transmission in health-care facilities (compared with risks observed in health-care facilities in other parts of the United States) occur together with an elevated prevalence among TB patients of *M. tuberculosis* strains that are resistant to both isoniazid and rifampin (*111–116*). Even in such situations, comprehensive application of infection control practices should be the primary strategy used to protect HCWs and others in the facility from infection with *M. tuberculosis*. BCG vaccination of HCWs should not be used as a primary TB control strategy because a) the protective efficacy of the vaccine in HCWs is uncertain; b) even if BCG vaccination is effective for a particular HCW, other persons in the health-care facility (e.g., patients, visitors, and other HCWs) are not protected against possible exposure to and infection with drug-resistant strains of *M. tuberculosis*; and c) BCG vaccination may complicate preventive therapy because of difficulties in distinguishing tuberculin skin test responses caused by infection with *M. tuberculosis* from those caused by the immune response to vaccination.

Hepatitis C and Other Parenterally Transmitted Non-A, Non-B Hepatitis

Hepatitis C virus (HCV) is the etiologic agent in most cases of parenterally transmitted non-A, non-B hepatitis in the United States (*117,118*). CDC estimates that the annual number of newly acquired HCV infections has ranged from 180,000 in 1984 to 28,000 in 1995. Of these, an estimated 2%–4% occurred among health-care personnel who were occupationally exposed to blood. At least 85% of persons who contract HCV

infection become chronically infected, and chronic hepatitis develops in an average of 70% of all HCV-infected persons (*117–119*). Up to 10% of parenterally transmitted non-A, non-B hepatitis may be caused by other bloodborne viral agents not yet characterized (non-ABCDE hepatitis) (*117,120*).

Serologic enzyme immunoassays (EIA) licensed for the detection of antibody to HCV (anti-HCV) have evolved since their introduction in 1990 and a third version is now available which detects anti-HCV in ≥95% of patients with HCV infection. Interpretation of EIA results is limited by several factors. These assays do not detect anti-HCV in all infected persons and do not distinguish among acute, chronic, or resolved infection. In 80% to 90% of HCV-infected persons, seroconversion occurs an average of 10–12 weeks after exposure to HCV. These screening assays also yield a high proportion (up to 50%) of falsely positive results when they are used in populations with a low prevalence of HCV infection (*118,121*). Although no true confirmatory test has been developed, supplemental tests for specificity are available (such as the licensed Recombinant Immunoblot Assay [RIBA™]), and should always be used to verify repeatedly reactive results obtained with screening assays.

The diagnosis of HCV infection also is possible by detecting HCV RNA with polymerase chain reaction (PCR) techniques. Although PCR assays for HCV RNA are available from several commercial laboratories on a research-use basis, results vary considerably between laboratories. In a recent study in which a reference panel containing known HCV RNA-positive and -negative sera was provided to 86 laboratories worldwide (*122*), only 50% were considered to have performed adequately (i.e., by failing to detect one weak positive sample), and only 16% reported faultless results. Both false-positive and false-negative results can occur from improper collection, handling, and storage of the test samples. In addition, because HCV RNA may be detectable only intermittently during the course of infection, a single negative PCR test result should not be regarded as conclusive. Tests also have been developed to quantitate HCV RNA in serum; however, the applicability of these tests in the clinical setting has not been determined.

Most HCV transmission is associated with direct percutaneous exposure to blood, and HCWs are at occupational risk for acquiring this viral infection (*123–131*). The prevalence of anti-HCV among hospital-based HCWs and surgeons is about 1%(*125–128*) and 2% among oral surgeons (*129,130*). In follow-up studies of HCWs who sustained percutaneous exposures to blood from anti-HCV positive patients through unintentional needlesticks or sharps injuries, the average incidence of anti-HCV seroconversion was 1.8% (range: 0%–7%) (*132–137*). In the only study that used PCR to measure HCV infection by detecting HCV RNA, the incidence of postinjury infection was 10% (*136*). Although these follow-up studies have not documented transmission associated with mucous membrane or nonintact skin exposures, one case report describes the transmission of HCV from a blood splash to the conjunctiva (*138*).

Several studies have examined the effectiveness of prophylaxis with immune globulins (IGs) in preventing posttransfusion non-A, non-B hepatitis (*139–141*). The findings of these studies are difficult to compare and interpret, because of lack of uniformity in diagnostic criteria, mixed sources of donors (volunteer and commercial), and differing study designs (some studies lacked blinding and placebo controls). In some of these studies, IGs appeared to reduce the rate of clinical disease but not overall infection rates. In one study, data indicated that chronic hepatitis was less likely to

develop in patients who received IG (*139*). None of these data have been reanalyzed since anti-HCV testing became available. In only one study was the first dose of IG administered after, rather than before, the exposure; the value of IG for postexposure prophylaxis is thus difficult to assess. The heterogeneous nature of HCV and its ability to undergo rapid mutation, however, appear to prevent development of an effective neutralizing immune response (*142*), suggesting that postexposure prophylaxis using IG is likely to be ineffective. Furthermore, IG is now manufactured from plasma that has been screened for anti-HCV. In an experimental study in which IG manufactured from anti-HCV negative plasma was administered to chimpanzees one hour after exposure to HCV, the IG did not prevent infection or disease (*143*).

The prevention of HCV infection with antiviral agents (e.g., alpha interferon) has not been studied. Although alpha interferon therapy is safe and effective for the treatment of chronic hepatitis C (*144*), the mechanisms of the effect are poorly understood. Interferon may be effective only in the presence of an established infection (*145*). Interferon must be administered by injection and may cause side effects. Based on these considerations, antiviral agents are not recommended for postexposure prophylaxis of HCV infection.

In the absence of effective prophylaxis, persons who have been exposed to HCV may benefit from knowing their infection status so they can seek evaluation for chronic liver disease and treatment. Sustained response rates to alpha interferon therapy generally are low (10%–20% in the United States). The occurrence of mild to moderate side effects in most patients has required discontinuation of therapy in up to 15% of patients. No clinical, demographic, serum biochemical, serologic, or histologic features have been identified that reliably predict which patients will sustain a long-term remission in response to alpha interferon therapy.

Several studies indicate that interferon treatment begun early in the course of HCV infection is associated with an increased rate of resolved infection. Onset of HCV infection among HCWs after exposure could be detected earlier by using PCR to detect HCV RNA than by using EIA to measure anti-HCV. However, PCR is not a licensed assay and its accuracy is highly variable. In addition, no data are available which indicate that treatment begun early in the course of chronic HCV infection is less effective than treatment begun during the acute phase of infection. Furthermore, alpha interferon is approved for the treatment of chronic hepatitis C only.

IG or antiviral agents are not recommended for postexposure prophylaxis of hepatitis C. No vaccine against hepatitis C is available. Health-care institutions should consider implementing policies and procedures to monitor HCWs for HCV infection after percutaneous or permucosal exposures to blood (*146*). At a minimum, such policies should include:

- For the source, baseline serologic testing for anti-HCV;
- For the person exposed to an anti-HCV positive source, baseline and follow-up (e.g., 6 months) serologic testing for anti-HCV and alanine aminotransferase activity;
- Confirmation by supplemental anti-HCV testing of all anti-HCV results reported as repeatedly reactive by EIA;

- Education of HCWs about the risk for and prevention of occupational transmission of all blood borne pathogens, including hepatitis C, using up-to-date and accurate information.

Other Diseases for Which Immunization of Health-Care Workers Is or May Be Indicated

Diseases are included in this section for one of the following reasons:

- Nosocomial transmission occurs, but HCWs are not at increased risk as a result of occupational exposure (i.e., hepatitis A),
- Occupational risk may be high, but protection via active or passive immunization is not available (i.e., pertussis), or
- Vaccines are available but are not routinely recommended for all HCWs or are recommended only in certain situations (i.e., vaccinia and meningococcal vaccines).

Hepatitis A

Occupational exposure generally does not increase HCWs' risk for hepatitis A virus (HAV) infection. When proper infection control practices are followed, nosocomial HAV transmission is rare. Outbreaks caused by transmission of HAV to neonatal intensive care unit staff by infants infected through transfused blood have occasionally been observed (*147–149*). Transmission of HAV from adult patients to HCWs is usually associated with fecal incontinence in the patients. However, most patients hospitalized with hepatitis A are admitted after onset of jaundice, when they are beyond the point of peak infectivity (*150*). Serologic surveys among many types of HCWs have not identified an elevated prevalence of HAV infection compared with other occupational populations (*151–153*).

Two specific prophylactic measures are available for protection against hepatitis A—administration of immune globulin (IG) and hepatitis A vaccine. When administered within 2 weeks after an exposure, IG is >85% effective in preventing hepatitis A (*2*). Two inactivated hepatitis A vaccines, which can provide long-term preexposure protection, were recently licensed in the United States: HAVRIX® (manufactured by SmithKline Beecham Biologicals) and VAQTA® (manufactured by Merck & Company, Inc.) (*2*). The efficacy of these vaccines in preventing clinical disease ranges from 94% to 100%. Data indicate that the duration of clinical protection conferred by VAQTA® is at least 3 years, and that conferred by HAVRIX® at least 4 years. Mathematical models of antibody decay indicate that protection conferred by vaccination may last up to 20 years (*2*).

Meningococcal Disease

Nosocomial transmission of *Neisseria meningitidis* is uncommon. In rare instances, direct contact with respiratory secretions of infected persons (e.g., during mouth-to-mouth resuscitation) has resulted in transmission from patients with meningococcemia or meningococcal meningitis to HCWs. Although meningococcal lower respiratory infections are rare, HCWs may be at increased risk for meningococcal in-

fection if exposed to *N. meningitidis*-infected patients with active productive coughs. HCWs can decrease the risk for infection by adhering to precautions to prevent exposure to respiratory droplets (*16,95*).

Postexposure prophylaxis is advised for persons who have had intensive, unprotected contact (i.e., without wearing a mask) with infected patients (e.g., intubating, resuscitating, or closely examining the oropharynx of patients)(*16*). Antimicrobial prophylaxis can eradicate carriage of *N. meningitidis* and prevent infections in persons who have unprotected exposure to patients with meningococcal infections (*9*). Rifampin is effective in eradicating nasopharyngeal carriage of *N. meningitidis*, but is not recommended for pregnant women, because the drug is teratogenic in laboratory animals. Ciprofloxacin and ceftriaxone in single-dose regimens are also effective in reducing nasopharyngeal carriage of *N. meningitidis,* and are reasonable alternatives to the multidose rifampin regimen (*9*). Ceftriaxone also can be used during pregnancy.

Although useful for controlling outbreaks of serogroup C meningococcal disease, administration of quadrivalent A,C,Y,W-135 meningococcal polysaccharide vaccines is of little benefit for postexposure prophylaxis (*9*). The serogroups A and C vaccines, which have demonstrated estimated efficacies of 85%–100% in older children and adults, are useful for control of epidemics (*9*). The decision to implement mass vaccination to prevent serogroup C meningococcal disease depends on whether the occurrence of more than one case of the disease represents an outbreak or an unusual clustering of endemic meningococcal disease. Surveillance for serogroup C disease and calculation of attack rates can be used to identify outbreaks and determine whether use of meningococcal vaccine is warranted. Recommendations for evaluating and managing suspected serogroup C meningococcal disease outbreaks have been published (*9*).

Pertussis

Pertussis is highly contagious. Secondary attack rates among susceptible household contacts exceed 80% (*154,155*). Transmission occurs by direct contact with respiratory secretions or large aerosol droplets from the respiratory tract of infected persons. The incubation period is generally 7–10 days. The period of communicability starts with the onset of the catarrhal stage and extends into the paroxysmal stage. Vaccinated adolescents and adults, whose immunity wanes 5–10 years after the last dose of vaccine (usually administered at age 4–6 years), are an important source of pertussis infection for susceptible infants. The disease can be transmitted from adult patients to close contacts, especially unvaccinated children. Such transmission may occur in households and hospitals.

Transmission of pertussis in hospital settings has been documented in several reports (*156–159*). Transmission has occurred from a hospital visitor, from hospital staff to patients, and from patients to hospital staff. Although of limited size (range: 2–17 patients and 5–13 staff), documented outbreaks were costly and disruptive. In each outbreak, larger numbers of staff were evaluated for cough illness and required nasopharyngeal cultures, serologic tests, prophylactic antibiotics, and exclusion from work.

During outbreaks that occur in hospitals, the risk for contracting pertussis among patients or staff is often difficult to quantify because exposure is not well defined.

Serologic studies conducted among hospital staff during two outbreaks indicate that exposure to pertussis is much more frequent than the attack rates of clinical disease indicate (*154,156–159*). Seroprevalence of pertussis agglutinating antibodies correlated with the degree of patient contact and was highest among pediatric house staff (82%) and ward nurses (71%), lowest among nurses with administrative responsibilities (35%) (*158*).

Prevention of pertussis transmission in health-care settings involves diagnosis and early treatment of clinical cases, respiratory isolation of infectious patients who are hospitalized, exclusion from work of staff who are infectious, and postexposure prophylaxis. Early diagnosis of pertussis, before secondary transmission occurs, is difficult because the disease is highly communicable during the catarrhal stage, when symptoms are still nonspecific. Pertussis should be one of the differential diagnoses for any patient with an acute cough illness of ≥7 days duration without another apparent cause, particularly if characterized by paroxysms of coughing, posttussive vomiting, whoop, or apnea. Nasopharyngeal cultures should be obtained if possible.

Precautions to prevent respiratory droplet transmission or spread by close or direct contact should be employed in the care of patients admitted to hospital with suspected or confirmed pertussis (*95*). These precautions should remain in effect until patients are clinically improved and have completed at least 5 days of appropriate antimicrobial therapy. HCWs in whom symptoms (i.e., unexplained rhinitis or acute cough) develop after known pertussis exposure may be at risk for transmitting pertussis and should be excluded from work (*16*)(see Other Considerations in Vaccination of Health-Care Workers—Work Restrictions for Susceptible Workers After Exposure).

One acellular pertussis vaccine is immunogenic in adults, but does not increase risk for adverse events when administered with tetanus and diphtheria (Td) toxoids, as compared with administration of Td alone (*160*). Recommendations for use of licensed diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccines among infants and young children have been published (*161*). If acellular pertussis vaccines are licensed for use in adults in the future, booster doses of adult formulations of acellular pertussis vaccines may be recommended to prevent the occurrence and spread of the disease in adults, including HCWs. However, acellular pertussis vaccines combined with diphtheria and tetanus toxoids (DTaP) will need to be reformulated for use in adults, because all infant formulations contain more diphtheria toxoid than is recommended for persons aged ≥7 years. Recommendations regarding routine vaccination of adults will require additional studies (e.g., studies of the incidence, severity, and cost of pertussis among adults; studies of the efficacy and safety of adult formulations of DTaP; and studies of the effectiveness and cost-effectiveness of a strategy of adult vaccination, particularly for HCWs).

Typhoid

The incidence of typhoid fever declined steadily in the United States from 1900 to 1960 and has remained at a low level. During 1985–1994, the average number of cases reported annually was 441 (CDC, unpublished data). The median age of persons with cases of typhoid was 24 years; 53% were male. Nearly three quarters of patients infected with *Salmonella typhi* reported foreign travel during the 30 days before onset of symptoms. During this ten year period, several cases of laboratory-acquired typhoid fever were reported among microbiology laboratory workers, only one of

whom had been vaccinated (*162*). *S. typhi* and other enteric pathogens may be nosocomially transmitted via the hands of personnel who are infected. Generally, personal hygiene, particularly hand washing before and after all patient contacts, will minimize risk for transmitting enteric pathogens to patients. If HCWs contract an acute diarrheal illness accompanied by fever, cramps, or bloody stools, they are likely to be excreting large numbers of infective organisms in their feces. Excluding these workers from care of patients until the illness has been evaluated and treated will prevent transmission (*16*).

Vaccinia

Vaccinia (smallpox) vaccine is a highly effective immunizing agent that brought about the global eradication of smallpox. In 1976, routine vaccinia vaccination of HCWs in the United States was discontinued. More recently, ACIP recommended use of vaccinia vaccine to protect laboratory workers from orthopoxvirus infection (*10*). Because studies of recombinant vaccinia virus vaccines have advanced to the stage of clinical trials, some physicians and nurses may now be exposed to vaccinia and recombinant vaccinia viruses. Vaccinia vaccination of these persons should be considered in selected instances (e.g., for HCWs who have direct contact with contaminated dressings or other infectious material).

Other Vaccine-Preventable Diseases

HCWs are not at greater risk for diphtheria, tetanus, and pneumococcal disease than the general population. ACIP recommends that all adults be protected against diphtheria and tetanus, and recommends pneumococcal vaccination of all persons aged ≥65 years and of younger persons who have certain medical conditions (see Recommendations).

Immunizing Immunocompromised Health-Care Workers

A physician must assess the degree to which an individual health-care worker is immunocompromised. Severe immunosuppression can be the result of congenital immunodeficiency; HIV infection; leukemia; lymphoma; generalized malignancy; or therapy with alkylating agents, antimetabolites, radiation, or large amounts of corticosteroids. All persons affected by some of these conditions are severely immunocompromised, whereas for other conditions (e.g., HIV infection), disease progression or treatment stage determine the degree of immunocompromise. A determination that an HCW is severely immunocompromised ultimately must be made by his or her physician. Immunocompromised HCWs and their physicians should consider the risk for exposure to a vaccine-preventable disease together with the risks and benefits of vaccination.

Corticosteroid Therapy

The exact amount of systemically absorbed corticosteroids and the duration of administration needed to suppress the immune system of an otherwise healthy person are not well defined. Most experts agree that steroid therapy usually does not contraindicate administration of live virus vaccines such as MMR and its component vaccines when therapy is a) short term (i.e., <14 days) low to moderate dose; b) low to

moderate dose administered daily or on alternate days; c) long-term alternate day treatment with short-acting preparations; d) maintenance physiologic doses (replacement therapy); or e) administered topically (skin or eyes), by aerosol, or by intra-articular, bursal, or tendon injection. Although the immunosuppressive effects of steroid treatment vary, many clinicians consider a steroid dose that is equivalent to or greater than a prednisone dose of 20 mg per day sufficiently immunosuppressive to cause concern about the safety of administering live virus vaccines. Persons who have received systemic corticosteroids in excess of this dose daily or on alternate days for an interval of ≥14 days should avoid vaccination with MMR and its component vaccines for at least 1 month after cessation of steroid therapy. Persons who have received prolonged or extensive topical, aerosol, or other local corticosteroid therapy that causes clinical or laboratory evidence of systemic immunosuppression also should not receive MMR, its component vaccines, and varicella vaccine for at least 1 month after cessation of therapy. Persons who receive corticosteroid doses equivalent to ≥20 mg per day or prednisone during an interval of <14 days generally can receive MMR or its component vaccines immediately after cessation of treatment, although some experts prefer waiting until 2 weeks after completion of therapy. Persons who have a disease that, in itself, suppresses the immune response and who are also receiving either systemic or locally administered corticosteroids generally should not receive MMR, its component vaccines, or varicella vaccine.

HIV-Infected Persons

In general, symptomatic HIV-infected persons have suboptimal immunologic responses to vaccines (*163–167*). The response to both live and killed antigens may decrease as the disease progresses (*167*). Administration of higher doses of vaccine or more frequent boosters to HIV-infected persons may be considered. However, because neither the initial immune response to higher doses of vaccine nor the persistence of antibody in HIV-infected patients has been systematically evaluated, recommendations cannot be made at this time.

Limited studies of MMR immunization in both asymptomatic and symptomatic HIV-infected patients who did not have evidence of severe immunosuppression documented no serious or unusual adverse events after vaccination (*168*). HIV-infected persons are at increased risk for severe complications if infected with measles. Therefore, MMR vaccine is recommended for all asymptomatic HIV-infected HCWs who do not have evidence of severe immunosuppression. Administration of MMR to HIV-infected HCWs who are symptomatic but do not have evidence of severe immunosuppression also should be considered. However, measles vaccine is not recommended for HIV-infected persons who have evidence of severe immunosuppression because a) a case of progressive measles pneumonia has been reported after administration of MMR vaccine to a person with AIDS and severe immunosuppression (*169*), b) the incidence of measles in the United States is currently very low (*170*), c) vaccination-related morbidity has been reported in severely immunocompromised persons who were not HIV-infected (*171*), and d) a diminished antibody response to measles vaccination occurs among severely immunocompromised HIV-infected persons (*172*).

RECOMMENDATIONS

Recommendations for administration of vaccines and other immunobiologic agents to HCWs are organized in three broad disease categories:

- those for which active immunization is strongly recommended because of special risks for HCWs (i.e., hepatitis B, influenza, measles, mumps, rubella, and varicella);
- those for which active and/or passive immunization of HCWs may be indicated in certain circumstances (i.e., tuberculosis, hepatitis A, meningococcal disease, typhoid fever, and vaccinia) or in the future (i.e.,pertussis); and
- those for which immunization of all adults is recommended (i.e., tetanus, diphtheria, and pneumococcal disease).

Immunization Is Strongly Recommended

ACIP strongly recommends that all HCWs be vaccinated against (or have documented immunity to) hepatitis B, influenza, measles, mumps, rubella, and varicella (Table 2). Specific recommendations for use of vaccines and other immunobiologics to prevent these diseases among HCWs follow.

Hepatitis B

Any HCW who performs tasks involving contact with blood, blood-contaminated body fluids, other body fluids, or sharps should be vaccinated. Hepatitis B vaccine should always be administered by the intramuscular route in the deltoid muscle with a needle 1–1.5 inches long.

Among health-care professionals, risks for percutaneous and permucosal exposures to blood vary during the training and working career of each person but are often highest during the professional training period. Therefore, vaccination should be completed during training in schools of medicine, dentistry, nursing, laboratory technology, and other allied health professions, before trainees have contact with blood. In addition, the OSHA Federal Standard requires employers to offer hepatitis B vaccine free of charge to employees who are occupationally exposed to blood or other potentially infectious materials (*27*).

Prevaccination serologic screening for previous infection is not indicated for persons being vaccinated because of occupational risk unless the hospital or health-care organization considers screening cost-effective. Postexposure prophylaxis with hepatitis B immune globulin (HBIG) (passive immunization) and/or vaccine (active immunization) should be used when indicated (e.g., after percutaneous or mucous membrane exposure to blood known or suspected to be HBsAg-positive [Table 3]).

Needlestick or other percutaneous exposures of unvaccinated persons should lead to initiation of the hepatitis B vaccine series. Postexposure prophylaxis should be considered for any percutaneous, ocular, or mucous membrane exposure to blood in the workplace and is determined by the HBsAg status of the source and the vaccination and vaccine-response status of the exposed person (Table 3)(*1,18*).

If the source of exposure is HBsAg-positive and the exposed person is unvaccinated, HBIG also should be administered as soon as possible after exposure

TABLE 3. Recommended postexposure prophylaxis for percutaneous or permucosal exposure to hepatitis B virus, United States

Vaccination and antibody response status of exposed person	Treatment when source is		
	HBsAG* positive	HBsAg negative	Source not tested or status unknown
Unvaccinated	HBIG† x 1; initiate HB vaccine series §	Initiate HB vaccine series	Initiate HB vaccine series
Previously vaccinated:			
Known responder¶	No treatment	No treatment	No treatment
Known non-responder	HBIG x 2 or HBIG x 1 and initiate revaccination	No treatment	If known high-risk source, treat as if source were HBsAg positive
Antibody response unknown	Test exposed person for anti-HBs** 1. If adequate¶, no treatment 2. If inadequate¶, HBIG x 1 and vaccine booster	No treatment	Test exposed person for anti-HBs 1. If adequate¶, no treatment 2. If inadequate¶, initiate revaccination

*Hepatitis B surface antigen.
†Hepatitis B immune globulin; dose 0.06 mL/kg intramuscularly.
§Hepatitis B vaccine.
¶Responder is defined as a person with adequate levels of serum antibody to hepatitis B surface antigen (i.e., anti-HBs ≥ 10 mIU/mL); inadequate response to vaccination defined as serum anti-HBs < 10 mIU/mL.
**Antibody to hepatitis B surface antigen.

(preferably within 24 hours) and the vaccine series started. The effectiveness of HBIG when administered >7 days after percutaneous or permucosal exposures is unknown. If the exposed person had an adequate antibody response (≥10 mIU/mL) documented after vaccination, no testing or treatment is needed, although administration of a booster dose of vaccine can be considered.

One to 2 months after completion of the 3-dose vaccination series, HCWs who have contact with patients or blood and are at ongoing risk for injuries with sharp instruments or needlesticks should be tested for antibody to hepatitis B surface antigen (anti-HBs). Persons who do not respond to the primary vaccine series should complete a second three-dose vaccine series or be evaluated to determine if they are HBsAg-positive. Revaccinated persons should be retested at the completion of the second vaccine series. Persons who prove to be HBsAg-positive should be counseled accordingly (*1,16,121,173*). Primary non-responders to vaccination who are HBsAg-negative should be considered susceptible to HBV infection and should be counseled regarding precautions to prevent HBV infection and the need to obtain HBIG prophylaxis for any known or probable parenteral exposure to HBsAg-positive blood (Table 3). Booster doses of hepatitis B vaccine are not considered necessary, and periodic serologic testing to monitor antibody concentrations after completion of the vaccine series is not recommended.

Influenza

To reduce staff illnesses and absenteeism during the influenza season and to reduce the spread of influenza to and from workers and patients, the following HCWs should be vaccinated in the fall of each year:

- Persons who attend patients at high risk for complications of influenza (whether the care is provided at home or in a health-care facility) (*3*);
- Persons aged ≥65 years; and
- Persons with certain chronic medical conditions (e.g., persons who have chronic disorders of the cardiovascular or pulmonary systems; persons who required medical follow-up or hospitalization within the preceding year because of chronic metabolic disease [including diabetes], renal dysfunction, hemoglobinopathies, or immunosuppression [including HIV infection]).
- Pregnant women who will be in the second or third trimester of pregnancy during influenza season.

Measles, Mumps, and Rubella

Persons who work within medical facilities should be immune to measles and rubella. Immunity to mumps is highly desirable for all HCWs. Because any HCW (i.e., medical or nonmedical, paid or volunteer, full time or part time, student or nonstudent, with or without patient-care responsibilities) who is susceptible can, if exposed, contract and transmit measles or rubella, all medical institutions (e.g., inpatient and outpatient, public and private) should ensure that those who work within their facilities* are immune to measles and rubella. Likewise, HCWs have a responsibility to avoid causing harm to patients by preventing transmission of these diseases.

Persons born in 1957 or later can be considered immune to measles, mumps, or rubella† only if they have documentation of a) physician-diagnosed measles or mumps disease; or b) laboratory evidence of measles, mumps, or rubella immunity (persons who have an "indeterminate" level of immunity upon testing should be considered nonimmune); or c) appropriate vaccination against measles, mumps, and rubella (i.e., administration on or after the first birthday of two doses of live measles vaccine separated by ≥28 days, at least one dose of live mumps vaccine, and at least one dose of live rubella vaccine).

Although birth before 1957 generally is considered acceptable evidence of measles and rubella immunity, health-care facilities should consider recommending a dose of MMR vaccine to unvaccinated workers born before 1957 who are in either of the following categories: a) those who do not have a history of measles disease or laboratory evidence of measles immunity, and b) those who lack laboratory evidence of rubella immunity. Rubella vaccination or laboratory evidence of rubella immunity is particularly important for female HCWs born before 1957 who can become pregnant.

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*A possible exception might be an outpatient facility that deals exclusively with elderly patients considered at low risk for measles.

†Birth before 1957 is not acceptable evidence of rubella immunity for women who can become pregnant because rubella can occur in some unvaccinated persons born before 1957 and because congenital rubella syndrome can occur in offspring of women infected with rubella during pregnancy.

Serologic screening need not be done before vaccinating against measles and rubella unless the health-care facility considers it cost-effective *(174–176)*. Serologic testing is not necessary for persons who have documentation of appropriate vaccination or other acceptable evidence of immunity to measles and rubella. Serologic testing before vaccination is appropriate only if tested persons identified as nonimmune are subsequently vaccinated in a timely manner, and should **not** be done if the return and timely vaccination of those screened cannot be ensured (*176*). Likewise, during outbreaks of measles, rubella, or mumps, serologic screening before vaccination is not recommended because rapid vaccination is necessary to halt disease transmission.

Measles-mumps-rubella (MMR) trivalent vaccine is the vaccine of choice. If the recipient has acceptable evidence of immunity to one or more of the components, monovalent or bivalent vaccines may be used. MMR or its component vaccines should not be administered to women known to be pregnant. For theoretical reasons, a risk to the fetus from administration of live virus vaccines cannot be excluded. Therefore, women should be counseled to avoid pregnancy for 30 days after administration of monovalent measles or mumps vaccines and for 3 months after administration of MMR or other rubella-containing vaccines. Routine precautions for vaccinating postpubertal women with MMR or its component vaccines include a) asking if they are or may be pregnant, b) not vaccinating those who say they are or may be pregnant, and c) vaccinating those who state that they are not pregnant after the potential risk to the fetus is explained. If a pregnant woman is vaccinated or if a woman becomes pregnant within 3 months after vaccination, she should be counseled about the theoretical basis of concern for the fetus, but MMR vaccination during pregnancy should not ordinarily be a reason to consider termination of pregnancy. Rubella-susceptible women from whom vaccine is withheld because they state they are or may be pregnant should be counseled about the potential risk for congenital rubella syndrome and the importance of being vaccinated as soon as they are no longer pregnant. Measles vaccine is not recommended for HIV-infected persons with evidence of severe immunosuppression (see Vaccination of HIV-Infected Persons).

Varicella

All HCWs should ensure that they are immune to varicella. Varicella immunization is particularly recommended for susceptible HCWs who have close contact with persons at high risk for serious complications, including a) premature infants born to susceptible mothers, b) infants who are born at <28 weeks of gestation or who weigh ≤1,000 g at birth (regardless of maternal immune status), c) pregnant women, and d) immunocompromised persons.

Serologic screening for varicella immunity need not be done before vaccinating unless the health-care institution considers it cost-effective. Routine postvaccination testing of HCWs for antibodies to varicella is not recommended because ≥90% of vaccinees are seropositive after the second dose of vaccine.

Hospitals should develop guidelines for management of vaccinated HCWs who are exposed to natural varicella. Seroconversion after varicella vaccination does not always result in full protection against disease. Therefore, the following measures should be considered for HCWs who are exposed to natural varicella: a) serologic testing for varicella antibody immediately after VZV exposure; b) retesting 5–6 days later

to determine if an anamnestic response is present; and c) possible furlough or reassignment of personnel who do not have detectable varicella antibody. Whether postexposure vaccination protects adults is not known.

Hospitals also should develop guidelines for managing HCWs after varicella vaccination because of the risk for transmission of vaccine virus. Institutions may wish to consider precautions for personnel in whom a rash develops after vaccination and for other vaccinated HCWs who will have contact with susceptible persons at high risk for serious complications.

Hepatitis C and Other Parenterally Transmitted Non-A, Non-B Hepatitis

No vaccine or other immunoprophylactic measures are available for hepatitis C or other parenterally transmitted non-A, non-B hepatitis. HCWs should follow recommended practices for preventing transmission of all blood borne pathogens (see Background—Hepatitis C and other Parenterally Transmitted Non-A, Non-B Hepatitis).

Other Diseases for Which Immunoprophylaxis Is or May Be Indicated

ACIP does not recommend routine immunization of HCWs against tuberculosis, hepatitis A, pertussis, meningococcal disease, typhoid fever, or vaccinia. However, immunoprophylaxis for these diseases may be indicated for HCWs in certain circumstances.

Tuberculosis and BCG Vaccination of Health-Care Workers in High-Risk Settings

BCG vaccination of HCWs should be considered on an individual basis in health-care settings where **all** of the following conditions are met:

- a high percentage of TB patients are infected with *M. tuberculosis* strains that are resistant to both isoniazid and rifampin; and
- transmission of such drug-resistant *M. tuberculosis* strains to HCWs is likely; and,
- comprehensive TB infection-control precautions have been implemented and have not been successful.

Vaccination with BCG should not be required for employment or for assignment in specific work areas.

BCG is not recommended for use in HIV-infected persons or persons who are otherwise immunocompromised. In health-care settings where there is a high risk for transmission of *M. tuberculosis* strains resistant to both isoniazid and rifampin, employees and volunteers who are infected with HIV or are otherwise immunocompromised should be fully informed about the risk for acquiring TB infection and disease and the even greater risk for development of active TB disease associated with immunosuppression.

HCWs considered for BCG vaccination should be counseled regarding the risks and benefits of both BCG vaccination and preventive therapy. They should be informed about the variable findings of research regarding the efficacy of BCG vaccination, the interference of BCG vaccination with diagnosis of newly acquired *M. tuberculosis* infection, and the possible serious complications of BCG vaccine in immunocompromised persons, especially those infected with HIV. They also should be informed about the lack of data regarding the efficacy of preventive therapy for *M. tuberculosis* infections caused by strains resistant to isoniazid and rifampin and the risks for drug toxicity associated with multidrug preventive-therapy regimens. If requested by the employee, employers should offer (but not compel) a work assignment in which an immunocompromised HCW would have the lowest possible risk for infection with *M. tuberculosis.*

HCWs who contract TB are a source of infection for other health-care personnel and patients. Immunocompromised persons are at increased risk for developing active disease after exposure to TB; therefore, managers of health-care facilities should develop written policies to limit activities that might result in exposure of immunocompromised employees to persons with active cases of TB.

BCG vaccination is not recommended for HCWs in low-risk settings. In most areas of the United States, most *M. tuberculosis* isolates (approximately 90%) are fully susceptible to isoniazid or rifampin or both, and the risk for TB transmission in health-care facilities is very low if adequate infection control practices are maintained.

Hepatitis A

Routine preexposure hepatitis A vaccination of HCWs and routine IG prophylaxis for hospital personnel providing care to patients with hepatitis A are not indicated. Rather, sound hygienic practices should be emphasized. Staff education should emphasize precautions regarding direct contact with potentially infective materials (e.g., hand washing).

In documented outbreaks of hepatitis A, administration of IG to persons who have close contact with infected patients (e.g., HCWs, other patients) is recommended. A single intramuscular dose (0.02 mL per kg) of IG is recommended as soon as possible and ≤2 weeks after exposure (*2*). The usefulness of hepatitis A vaccine in controlling outbreaks in health-care settings has not been investigated.

The following vaccination schedules are recommended for the vaccines available in the United States:

- HAVRIX®: for persons aged >18 years, two doses, the second administered 6–12 months after the first.
- VAQTA® : for persons aged >17 years, two doses, the second administered 6 months after the first.

Meningococcal Disease

Routine vaccination of civilians, including HCWs, is not recommended. HCWs who have intensive contact with oropharyngeal secretions of infected patients, and who do not use proper precautions (*95*) should receive antimicrobial prophylaxis with rifampin (or sulfonamides, if the organisms isolated are sulfonamide-sensitive). Ciprofloxacin and ceftriaxone are reasonable alternative drugs; ceftriaxone can be ad-

ministered to pregnant women. Vaccination with quadrivalent polysaccharide vaccine should be used to control outbreaks of serogroup C meningococcal disease. Surveillance for serogroup C disease and calculation of attack rates can be used to identify outbreaks and determine whether use of meningococcal vaccine is warranted.

Pertussis

Pertussis vaccines (whole-cell and acellular) are licensed for use only among children aged 6 weeks through 6 years. If acellular pertussis vaccines are licensed for use in adults in the future, booster doses of adult formulations may be recommended to prevent the occurrence and spread of the disease in HCWs.

Typhoid

Workers in microbiology laboratories who frequently work with *S. typhi* should be vaccinated with any one of the three typhoid vaccines distributed in the United States: oral live-attenuated Ty21a vaccine (one enteric-coated capsule taken on alternate days to a total of four capsules), the parenteral heat-phenol inactivated vaccine (two 0.5 mL subcutaneous doses, separated by ≥4 weeks), or the capsular polysaccharide parenteral vaccine (one 0.5 mL intramuscular dose). Under conditions of continued or repeated exposure to *S. typhi*, booster doses are required to maintain immunity, every 5 years if the oral vaccine is used, every 3 years if the heat-phenol inactivated parenteral vaccine is used, and every 2 years if the capsular polysaccharide vaccine is used. Live-attenuated Ty21a vaccine should not be used among immunocompromised persons, including those infected with HIV (*13*).

Vaccinia

Vaccinia vaccine is recommended only for the few persons who work with orthopoxviruses (e.g., laboratory workers who directly handle cultures or animals contaminated or infected with vaccinia, recombinant vaccinia viruses, or other orthopoxviruses that replicate readily in humans [e.g., monkeypox, cowpox, and others]). Other HCWs (e.g., physicians and nurses) whose contact with these viruses is limited to contaminated materials (e.g., dressings) and who adhere to appropriate infection control measures are at lower risk for accidental infection than laboratory workers, but may be considered for vaccination. When indicated, vaccinia vaccine should be administered every 10 years (*10*). Vaccinia vaccine should not be administered to immunocompromised persons (including persons infected with HIV), persons who have eczema or a history of eczema, or to pregnant women (*10*).

Other Vaccine-Preventable Diseases

Health-care workers are not at substantially increased risk than the general adult population for acquiring diphtheria, pneumococcal disease, or tetanus. Therefore, they should seek these immunizations from their primary care provider, according to ACIP recommendations (*12,14*).

Tetanus and Diphtheria

Primary vaccination of previously unvaccinated adults consists of three doses of adult tetanus-diphtheria toxoid (Td): 4–6 weeks should separate the first and second

doses; the third dose should be administered 6–12 months after the second (*12*). After primary vaccination, a tetanus-diphtheria (Td) booster is recommended for all persons every 10 years. HCWs should be encouraged to receive recommended Td booster doses.

Pneumococcal Disease

Persons for whom pneumococcal vaccine is recommended include:

- Persons aged ≥65 years.
- Persons aged ≥2 and <65 years who, because they have certain chronic illnesses, are at increased risk for pneumococcal disease, its complications, or severe disease if they become infected. Included are those who have chronic cardiovascular disease (i.e., congestive heart failure [CHF] or cardiomyopathies), chronic pulmonary disease (i.e., chronic obstructive pulmonary disease [COPD] or emphysema, but not asthma), diabetes mellitus, alcoholism, chronic liver disease (cirrhosis), or cerebrospinal fluid leaks.
- Persons ≥2 and <65 years of age with functional or anatomic asplenia (e.g., sickle cell disease, splenectomy).
- Persons ≥2 and <65 years of age living in special environments or social settings where an increased risk exists for invasive pneumococcal disease or its complications (e.g., Alaska Natives and certain American Indian populations).
- Immunocompromised persons ≥ 2 years of age, including
  - — persons infected with HIV and persons who have leukemia, lymphoma, Hodgkin's disease, multiple myeloma, generalized malignancy, chronic renal failure, nephrotic syndrome;
  - — persons with other conditions associated with immunosuppression (e.g., organ or bone marrow transplantation); and
  - — persons receiving immunosuppressive chemotherapy, including long-term systemic corticosteroids.

Immunization of Immunocompromised Health-Care Workers

ACIP has published recommendations for immunization of immunocompromised persons (*177*). ACIP recommendations for use of individual vaccines or immune globulins also should be consulted for additional information regarding the epidemiology of the diseases and the safety and the efficacy of the vaccines or immune globulin preparations. Specific recommendations for use of vaccines depend upon the type of immunocompromising condition (Table 4).

Killed or inactivated vaccines do not represent a danger to immunocompromised HCWs and generally should be administered as recommended for workers who are not immunocompromised. Additional vaccines, particularly bacterial polysaccharide vaccines (i.e., *Haemophilus influenzae* type b [Hib] vaccine, pneumococcal vaccine, and meningococcal vaccine), are recommended for persons whose immune function is compromised by anatomic or functional asplenia and certain other conditions. Fre-

TABLE 4. Summary of ACIP recommendations concerning immunization of health-care workers with special conditions

Vaccine	Pregnancy	HIV Infection	Severe Immuno-suppression*	Asplenia	Renal Failure	Diabetes	Alcoholism and Alcoholic Cirrhosis
BCG	C	C	C	UI	UI	UI	UI
Hepatitis A	UI	UI	UI	UI	UI	UI	R†
Hepatitis B	R	R	R	R	R	R	R
Influenza	R§	R	R	R	R	R	R
Measles, Mumps, Rubella	C	R¶	C	R	R	R	R
Meningococcus	UI	UI	UI	R†	UI	UI	UI
Poliovirus vaccine, inactivated (IPV)**	UI	UI	UI	UI	UI	UI	UI
Poliovirus vaccine, live, oral (OPV)**	UI	C	C	UI	UI	UI	UI
Pneumococcus†	UI	R	R	R	R	R	R
Rabies	UI	UI	UI	UI	UI	UI	UI
Tetanus/diphtheria†	R	R	R	R	R	R	R
Typhoid, Inactivated & V_i††	UI	UI	UI	UI	UI	UI	UI
Typhoid, Ty21a	UI	C	C	UI	UI	UI	UI
Varicella	C	C	C	R	R	R	R
Vaccinia	C	C	C	UI	UI	UI	UI

* Severe immunosuppression can be caused by congenital immunodeficiency, leukemia, lymphoma, generalized malignancy or therapy with alkylating agents, antimetabolites, ionizing radiation, or large amounts of corticosteroids.
† Recommendation is based on the person's underlying condition rather than occupation.
§ Women who will be in the second or third trimester of pregnancy during the influenza season.
¶ Contraindicated in HIV-infected persons who have evidence of severe immunosuppression.
** Vaccination is recommended for unvaccinated health-care workers who have close contact with patients who may be excreting wild polioviruses. Primary vaccination with IPV is recommended because the risk for vaccine-associated paralysis after administration of OPV is higher among adults than among children. Health care workers who have had a primary series of OPV or IPV who are directly involved with the provision of care to patients who may be excreting poliovirus may receive another dose of either IPV or OPV. Any suspected case of poliomyelitis should be investigated immediately. If evidence suggests transmission of wild poliovirus, control measures to contain further transmission should be instituted immediately, including an OPV vaccination campaign.
†† Capsular polysaccharide parenteral vaccine.
Abbreviations: R=Recommended; **C**= Contraindicated; **UI**=Use if indicated.

quently, the immune response of immunocompromised persons to these vaccine antigens is not as good as that of nonimmunocompromised persons; higher doses or more frequent boosters may be required. Even with these modifications, the immune response may be suboptimal.

HIV-Infected Persons

Specific recommendations for vaccination of HIV-infected persons have been developed (Table 4). In general, live virus or live bacterial vaccines should not be administered to HIV-infected persons. However, asymptomatic HCWs need not be tested for HIV infection before administering live virus vaccines.

The following recommendations apply to all HCWs infected with HIV:

- MMR vaccine is recommended for all asymptomatic HIV-infected HCWs who do not have evidence of severe immunosuppression. Administration of MMR to HIV-infected HCWs who are symptomatic, but who do not have evidence of severe immunosuppression, should be considered. Measles vaccine is not recommended for HIV-infected persons with evidence of severe immunosuppression.
- Enhanced inactivated poliovirus vaccine (IPV) is the **only** poliovirus vaccine recommended for HIV-infected persons (*11*). Live oral poliovirus vaccine (OPV) **should not** be administered to immunocompromised persons.
- Influenza and pneumococcal vaccines are indicated for all HIV-infected persons (influenza vaccination for persons aged $\geq$ 6 months and pneumococcal vaccination for persons aged $\geq$2 years).

OTHER CONSIDERATIONS IN VACCINATION OF HEALTH-CARE WORKERS

Other considerations important to appropriate immunoprophylaxis of HCWs include maintenance of complete immunization records, policies for catch-up vaccination of HCWs, work restrictions for susceptible employees who are exposed to vaccine-preventable diseases, and control of outbreaks of vaccine-preventable disease in health-care settings. Additional vaccines not routinely recommended for HCWs in the United States may be indicated for those who travel to certain other regions of the world to perform research or health-care work (e.g., as medical volunteers in a humanitarian effort).

Immunization Records

An immunization record should be maintained for each HCW. The record should reflect documented disease and vaccination histories as well as immunizing agents administered during employment. At each immunization encounter, the record should be updated and the HCW encouraged to maintain the record as appropriate (*15*).

Catch-Up Vaccination Programs

Managers of health-care facilities should consider implementing catch-up vaccination programs for HCWs who are already employed, in addition to policies to ensure

that newly hired HCWs receive necessary vaccinations. This strategy will help prevent outbreaks of vaccine preventable diseases (see Outbreak Control). Because education enhances the success of many immunization programs, reference materials should be available to assist in answering questions regarding the diseases, vaccines, and toxoids, and the program or policy being implemented. Conducting educational workshops or seminars several weeks before the initiation of the program may be necessary to ensure acceptance of program goals.

Work Restrictions for Susceptible Workers After Exposure

Postexposure work restrictions ranging from restriction of contact with high-risk patients to complete exclusion from duty are appropriate for HCWs who are not immune to certain vaccine-preventable diseases (Table 5). Recommendations concerning work restrictions in these circumstances have been published (*16,35,178*).

Outbreak Control

Hospitals should develop comprehensive policies and protocols for management and control of outbreaks of vaccine-preventable disease. Outbreaks of vaccine-preventable diseases are costly and disruptive. Outbreak prevention, by ensuring that all HCWs who have direct contact with patients are fully immunized, is the most effective and cost-effective control strategy. Disease-specific outbreak control measures are described in published ACIP recommendations (Table 1) (*1–15*) and infection control references (*16,35,95, 178–180*).

Vaccines Indicated for Foreign Travel

Hospital and other HCWs who perform research or health-care work in foreign countries may be at increased risk for acquiring certain diseases (e.g, hepatitis A, poliomyelitis, Japanese encephalitis, meningococcal disease, plague, rabies, typhoid, or yellow fever). Vaccinations against those diseases should be considered when indicated for foreign travel (*181*). Elevated risks for acquiring these diseases may stem from exposure to patients in health-care settings (e.g., poliomyelitis, meningococcal disease), but may also arise from circumstances unrelated to patient care (e.g, high endemicity of hepatitis A or exposure to arthropod disease vectors [yellow fever]).

TABLE 5. Work restrictions* for health-care workers (HCWs) exposed to or infected with certain vaccine-preventable diseases

Disease/Problem	Work Restriction	Duration
Diphtheria		
Active	Exclude from duty.	Until antimicrobial therapy is completed **and** 2 nasopharyngeal cultures obtained ≥24 hours apart are negative.
Postexposure		
(Susceptible HCWs; previously vaccinated HCWs who have not had a Td booster dose within the previous 5 years)	Exclude from duty.	Same as active diphtheria
Asymptomatic carriers	Exclude from duty.	Same as active diphtheria.
Hepatitis A	Restrict from patient contact and food handling.	7 days after onset of jaundice.
Hepatitis B		
HCWs with acute or chronic antigenemia:		
-HCWs who do not perform exposure-prone invasive procedures (*21*)	Standard precautions should always be observed. No restriction unless epidemiologically linked to transmission of infection.	Universal precautions should always be observed.
-HCWs who perform exposure-prone invasive procedures	These HCWs should not perform exposure-prone invasive procedures until they have sought counsel from an expert review panel which should review and recommend the procedures the worker can perform, taking into account the specific procedure as well as the skill and technique of the worker (*30*).	Until HBeAg† is negative.
Upper respiratory infections		
(Persons at high risk for complications of influenza as defined by ACIP [*3*])	During particular seasons (e.g., during winter when influenza and/or RSV are prevalent), consider excluding personnel with acute febrile upper respiratory infections (including influenza) from care of high-risk patients.	Until acute symptoms resolve.
Measles		
Active	Exclude from duty	7 days after rash appears.
Postexposure (Susceptible personnel)	Exclude from duty.	5th day after 1st exposure through 21st day after last exposure and/or 7 days after the rash appears.

TABLE 5. Work restrictions* for health-care workers (HCWs) exposed to or infected with certain vaccine-preventable diseases — Continued

Disease/Problem	Work Restriction	Duration
Mumps		
Active	Exclude from duty	9 days after onset of parotitis.
Postexposure (Susceptible personnel)	Exclude from duty.	12th day after 1st exposure through 26th day after last exposure **or** 9 days after onset of parotitis.
Pertussis		
Active	Exclude from duty	Beginning of catarrhal stage through 3rd week after onset of paroxysms or until 5 days after start of effective antimicrobial therapy.
Postexposure		
Symptomatic personnel	Exclude from duty	5 days after start of effective antimicrobial therapy.
Asymptomatic personnel	No restriction, on antimicrobial prophylactic therapy.	
Rubella		
Active	Exclude from duty	5 days after the rash appears.
Postexposure (Susceptible personnel)	Exclude from duty.	7th day after 1st exposure through 21st day after last exposure and/or 5 days after rash appears.
Varicella		
Active	Exclude from duty	Until all lesions dry and crust.
Postexposure (Susceptible personnel)	Exclude from duty	10th day after 1st exposure through 21st day (28th day if VZIG administered) after the last exposure; if varicella occurs, until all lesions dry and crust.
Zoster		
(Localized in normal person)	Cover lesions; restrict from care of high-risk patients[§].	Same as varicella.
Postexposure (Susceptible personnel)	Restrict from patient contact.	

*Adapted from:

- (*173*) CDC. Recommendations for preventing transmission of human immunodeficiency virus and hepatitis B virus to patients during exposure-prone invasive procedures. MMWR 1991;40(RR-8):1–8.

- (*95*) CDC. Guideline for isolation precautions in hospitals. Recommendations of the Hospital Infection Control Practices Advisory Committee (HICPAC) and the National Center for Infectious Diseases. Infect Control Hosp Epidemiol 1996;17:53–80.

- (*178*) Williams WW: CDC guideline for infection control in hospital personnel. Infect Control 1983;4(Suppl):326-49.

[†]HBeAg = Hepatitis B e antigen.

[§]Patients who are susceptible to varicella and at increased risk for complications of varicella (i.e., neonates and immunocompromised persons of any age.)

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ACIP Provisional Recommendations for the Use of Combination Vaccines

Date of ACIP vote: June 24, 2009
Date of posting of provisional recommendations: August 28, 2009

These provisional recommendations when published in the MMWR, will replace those of the 1999 MMWR Recommendation and Reports document: *Centers for Disease Control and Prevention. Combination Vaccines for Childhood Immunization: Recommendations of the Advisory Committee on Immunization Practices, the American Academy of Pediatrics (AAP), and the American Academy of Family Physicians (AAFP). MMWR 1999; 48(No. RR-5).*
The new recommendations apply to all age groups.

Definition of Combination Vaccine

A product whose components can be equally divided into independently available routine vaccines.

General Recommendations for Use

The use of a combination vaccine generally is preferred over separate injections of its equivalent component vaccines. Considerations should include provider assessment*, patient preference, and the potential for adverse events.

- Provider assessment should include the number of injections, vaccine availability, likelihood of improved coverage, likelihood of patient return, and storage and cost consideration.

These recommendations on use of combination vaccines will be included as a section in *General Recommendations on Immunization: Recommendations of the Advisory Committee on Immunization Practices (MMWR 2006;56(No.RR-15));* revision in preparation.

* Provider assessment should include the number of injections, vaccine availability, likelihood of improved coverage, likelihood of patient return, and storage and cost consideration.

This document available at: www.cdc.gov/vaccines/recs/provisional/default.htm

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Use of Combination Measles, Mumps, Rubella, and Varicella Vaccine

Recommendations of the Advisory Committee on Immunization Practices

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

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Use of Combination Measles, Mumps, Rubella, and Varicella Vaccine

Recommendations of the Advisory Committee on Immunization Practices (ACIP)

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Summary

This report presents new recommendations adopted in June 2009 by CDC's Advisory Committee on Immunization Practices (ACIP) regarding use of the combination measles, mumps, rubella, and varicella vaccine (MMRV, ProQuad, Merck & Co., Inc.). MMRV vaccine was licensed in the United States in September 2005 and may be used instead of measles, mumps, rubella vaccine (MMR, M-M-RII, Merck & Co., Inc.) and varicella vaccine (VARIVAX, Merck & Co., Inc.) to implement the recommended 2-dose vaccine schedule for prevention of measles, mumps, rubella, and varicella among children aged 12 months–12 years. At the time of its licensure, use of MMRV vaccine was preferred for both the first and second doses over separate injections of equivalent component vaccines (MMR vaccine and varicella vaccine), which was consistent with ACIP's 2006 general recommendations on use of combination vaccines (CDC. General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices [ACIP]. MMWR 2006;55;[No. RR-15]). Since July 2007, supplies of MMRV vaccine have been temporarily unavailable as a result of manufacturing constraints unrelated to efficacy or safety. MMRV vaccine is expected to be available again in the United States in May 2010.

In February 2008, on the basis of preliminary data from two studies conducted postlicensure that suggested an increased risk for febrile seizures 5–12 days after vaccination among children aged 12–23 months who had received the first dose of MMRV vaccine compared with children the same age who had received the first dose of MMR vaccine and varicella vaccine administered as separate injections at the same visit, ACIP issued updated recommendations regarding MMRV vaccine use (CDC. Update: recommendations from the Advisory Committee on Immunization Practices [ACIP] regarding administration of combination MMRV vaccine. MMWR 2008;57:258–60). These updated recommendations expressed no preference for use of MMRV vaccine over separate injections of equivalent component vaccines for both the first and second doses.

The final results of the two postlicensure studies indicated that among children aged 12–23 months, one additional febrile seizure occurred 5–12 days after vaccination per 2,300–2,600 children who had received the first dose of MMRV vaccine compared with children who had received the first dose of MMR vaccine and varicella vaccine administered as separate injections at the same visit. Data from postlicensure studies do not suggest that children aged 4–6 years who received the second dose of MMRV vaccine had an increased risk for febrile seizures after vaccination compared with children the same age who received MMR vaccine and varicella vaccine administered as separate injections at the same visit.

In June 2009, after consideration of the postlicensure data and other evidence, ACIP adopted new recommendations regarding use of MMRV vaccine for the first and second doses and identified a personal or family (i.e., sibling or parent) history of seizure as a precaution for use of MMRV vaccine. For the first dose of measles, mumps, rubella, and varicella vaccines at age 12–47 months, either MMR vaccine and varicella vaccine or MMRV vaccine may be used. Providers who are considering administering MMRV vaccine should discuss the benefits and risks of both vaccination options with the parents or caregivers. Unless the parent or caregiver expresses a preference for MMRV vaccine, CDC recommends that MMR vaccine and varicella vaccine should be administered for the first dose in this age group. For

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the second dose of measles, mumps, rubella, and varicella vaccines at any age (15 months–12 years) and for the first dose at age ≥48 months, use of MMRV vaccine generally is preferred over separate injections of its equivalent component vaccines (i.e., MMR vaccine and varicella vaccine). This recommendation is consistent with ACIP's 2009 provisional general recommendations regarding use of combination vaccines (available at http://www.cdc.gov/vaccines/recs/provisional/downloads/combo-vax-Aug2009-508.pdf), which state that use of a combination vaccine generally is preferred over its equivalent component vaccines.

Introduction

To prevent measles, mumps, rubella, and varicella, the Advisory Committee on Immunization Practices (ACIP) recommends a 2-dose vaccine schedule in childhood, with the first dose administered at age 12–15 months and the second dose at age 4–6 years (*1,2*). In September 2005, the combination quadrivalent measles, mumps, rubella, and varicella vaccine (MMRV, ProQuad, Merck & Co., Inc.) was licensed by the Food and Drug Administration for use among children aged 12 months–12 years, and indications for its use were published subsequently (*3*). The availability of MMRV vaccine meant that two vaccination options were available to implement the ACIP recommendation for vaccination of children aged 12 months–12 years: 1) trivalent measles, mumps, rubella vaccine (MMR, M-M-RII, Merck & Co., Inc.) and monovalent varicella vaccine (VARIVAX, Merck & Co., Inc.) administered as two separate injections or 2) combination MMRV vaccine administered as one injection. Consistent with ACIP's 2006 general recommendations on immunization, use of the combination MMRV vaccine was preferred over separate injections of equivalent component vaccines (MMR vaccine and varicella vaccine) (*2,3*). Since July 2007, supplies of MMRV vaccine have been temporarily unavailable as a result of manufacturing constraints unrelated to efficacy or safety (i.e., lower-than-expected yields of bulk varicella-zoster virus in production lots) (*4,5*). MMRV vaccine is expected to be available again in the United States in May 2010.

The two vaccination options are considered to provide the same protection against the four diseases. In MMRV vaccine prelicensure studies conducted among children aged 12–23 months, fever and rash had been reported at a greater rate 0–42 days following vaccination among children who received a first dose of MMRV vaccine (n = 4,497) than among children who received first doses of MMR vaccine and varicella vaccine (n = 2,038) (*6*). In light of these findings, to evaluate if an increased risk for febrile seizures might be associated with the first dose of MMRV vaccine, CDC and Merck initiated separate postlicensure studies. Preliminary data from these two studies presented to ACIP in February 2008 suggested a 2.3-times higher risk for febrile seizures among children aged 12–23 months during the 5–12 or 7–10 days after administration of the first dose of MMRV vaccine compared with administration of the first dose of MMR vaccine and varicella vaccine at the same time (*7*). On the basis of these preliminary data, in February 2008, ACIP issued updated recommendations expressing no preference for use of MMRV vaccine over separate injections of equivalent component vaccines (i.e., MMR vaccine and varicella vaccine) for both the first and second dose (*7*). ACIP also established a workgroup to evaluate postlicensure and other safety data regarding the risk for febrile seizures after MMRV vaccine and formulate policy options for use of MMRV vaccine for consideration by ACIP.

In June 2009, after consideration of final data from the postlicensure studies and other evidence, ACIP adopted new recommendations regarding use of MMRV vaccine. This report provides these recommendations and replaces the 2008 recommendations for the use of MMRV vaccine (*7*).

Methods

The ACIP MMRV Vaccine Safety Workgroup was formed in spring 2008 and included federal and nonfederal experts from diverse backgrounds, including vaccine safety; epidemiology and vaccines related to measles, mumps, rubella, and varicella; statistics and pharmacoepidemiology; clinical pediatric neurology, infectious diseases, and primary care; and vaccinology and vaccine policy. The workgroup also sought input from partner organizations (e.g., the American Academy of Pediatrics and the American Academy of Family Physicians) and from local and state health departments. In addition, members of the CDC Public Health Ethics Committee and members of the Ethics Subcommittee of the Advisory Committee to the CDC Director (http://www.cdc.gov/od/science/phethics) were consulted.

The workgroup reviewed findings from two unpublished (at the time of discussions, June 12, 2008–June 24, 2009) postlicensure studies on MMRV vaccine and risk for febrile seizures; prelicensure MMRV vaccine data; literature regarding MMR vaccine and varicella vaccine immunogenicity, efficacy, effectiveness, and safety; measles, mumps, rubella, and varicella disease burden; the epidemiology of febrile seizures; the medical and psychosocial importance of febrile seizures; and program implementation considerations. The workgroup also reviewed data on provider and parental attitudes regarding multiple injections and the use of MMRV vaccine in the

context of an increased risk for febrile seizures after the first dose of MMRV vaccine.

Each member of the ACIP workgroup provided their individual interpretation of febrile seizure risk data and input on proposed policy options through two surveys that were subsequently discussed and compiled. In June 2009, ACIP discussed the safety evidence for MMRV vaccine and febrile seizure risk and risk-benefit interpretation and approved policy recommendations for the use of MMRV vaccine compared with MMR vaccine and varicella vaccine. CDC provided guidance regarding implementation of these recommendations.

Scientific Evidence Relevant for Decision-Making

Vaccine Safety

Risk for Febrile Seizure After First Dose of MMRV Vaccine

MMR vaccine is associated with an increased risk for febrile seizures during the first 2 weeks after vaccination (*8*) when the peak in replication of the live attenuated measles virus occurs (6–12 days) (*9*). This risk period has been defined variably in clinical and epidemiologic studies as 8–14 days, 7–12 days, or 5–12 days (*8,10,11*).

In the MMRV vaccine prelicensure studies conducted among children aged 12–23 months, two systemic vaccine-related adverse reactions were reported at a significantly greater rate 0–42 days following vaccination in children who received a first dose of MMRV vaccine (n = 4,497) than in children who received first doses of MMR vaccine and varicella vaccine (n = 2,038) (*6*). Fever (reported as abnormal or elevated ≥102°F [≥39°C] oral equivalent) was observed in 21.5% of MMRV vaccine recipients compared with 14.9% of MMR vaccine and varicella vaccine recipients (risk difference [RD]: 6.6%; 95% confidence interval [CI] = 4.6–8.5). Measles-like rash was observed in 3.0% of MMRV vaccine recipients compared with 2.1% of those receiving MMR vaccine and varicella vaccine (RD: 1.0%; CI = 0.1–1.8) (*6*). Both of these adverse events were reported to occur more frequently 5–12 days postvaccination and typically resolved spontaneously without sequelae.

The reasons for a higher rate of vaccine-associated fever or measles-like rashes after the first dose of MMRV vaccine are not fully understood but might suggest a more vigorous immune response in response to an increase in measles virus replication. The measles, mumps, and rubella viruses in MMRV vaccine are identical and of equal potency to those in the MMR vaccine, but the potency of the varicella-zoster virus is at least seven times higher than the potency in the monovalent varicella vaccine (a minimum of 3.99 $\log_{10}$ plaque forming units [PFUs] compared with 3.13 $\log_{10}$ PFUs) (*6*). However, the measles geometric mean titers (GMTs) measured 6 weeks after vaccination were higher among children who received the first dose of MMRV vaccine than among children who received the first dose of MMR vaccine and varicella vaccine administered at the same visit, whereas the varicella GMTs were similar (*12*). Statistical modeling indicated that the level of the measles antibody titer after receipt of MMRV vaccine was associated positively with the rate of fever and the rate of measles-like rashes (*13*).

Because of the known association between fever and febrile seizures (*14*), Merck and CDC sponsored separate postlicensure studies among larger populations of vaccinated children than were feasible during prelicensure studies to evaluate if a risk for febrile seizures might be associated with the first dose of MMRV vaccine. These studies assessed the febrile seizure risk in different populations using different methods.

Merck sponsored a postlicensure cohort study among children aged 12–60 months (99% of whom were aged 12–23 months) enrolled in a large managed care organization (MCO) (*11*). All potential cases identified by *International Classification of Diseases, Ninth Revision* (ICD-9) codes for seizure from electronic medical records (779.0 [neonatal seizures], 333.2 [myoclonus], 345 [epilepsy], 780.3 [convulsion], 780.31 [simple febrile convulsion], 780.32 [complex febrile convulsion], and 780.39 [other convulsion]) were adjudicated by an independent committee using the Brighton Collaboration definition for seizure (*15*) and documentation of fever (whether measured or not) in the chart. The study groups included 31,298 children who received a first dose of MMRV vaccine during February 2006–June 2007 and 31,298 children who received a first dose of MMR vaccine and varicella vaccine at the same visit during November 2003–January 2006. The two groups were matched individually by age, sex, and calendar date of vaccination. On the basis of findings on fever from prelicensure trials, the primary period of interest to assess the risk for febrile seizures was 5–12 days after vaccination. Another prespecified period of interest was 0–30 days after vaccination because of the biologic plausibility that the replication of the component viruses of the MMRV vaccine might occur during the month after vaccination. The relative risk (RR) for febrile seizures 5–12 days after vaccination was 2.2 (CI = 1.0–4.7; $p<0.05$) among children who received the first dose of MMRV vaccine (rate: 7.0 per 10,000 vaccinations) compared with children who received the first dose of MMR vaccine and varicella vaccine administered at the same visit (rate: 3.2 per 10,000 vaccinations) (Table). These results suggest that, during the 5–12 day postvaccination period, approximately one additional febrile seizure occurred

TABLE. Summary results from Vaccine Safety Datalink (VSD) and Merck-sponsored studies for febrile seizure after the first dose of measles, mumps, rubella and varicella vaccine (MMRV) compared with the first dose of measles, mumps, rubella vaccine (MMR) and varicella vaccine (V) administered at the same visit — United States, 2009

Characteristic	VSD*	Merck-sponsored†
Age/No. subjects, by vaccine	All aged 12–23 months MMRV: n = 83,107 MMR and V: n= 376,354	99% aged 12–23 months MMRV: n = 31,298 MMR and V: n = 31,298
Postvaccination interval		
Week 1–2	7–10 days§ RR: 2.0 (CI = 1.4–2.9) AR: 4.3 per 10,000 (CI = 2.6–5.6)	5–12 days§ RR: 2.2 (CI = 1.0–4.7) AR: 3.8 per 10,000 (CI = 0.3–7.4)
Week 1–6	0–42 days§ RR: 1.5 (CI = 1.1–1.9) AR: 6.2 per 10,000 (CI = 2.0–9.5)	0–30 days RR: 1.1 (CI = 0.7–1.7) AR: 1.3 per 10,000 (CI = -4.5–7.0)

RR = relative risk; AR = attributable risk; CI = 95% confidence interval.
* **Source:** Klein NP, Fireman B, Yih WK, et al. Measles-mumps-rubella-varicella combination vaccine and the risk of febrile seizures. Pediatrics 2010. In press.
† **Source:** Jacobsen SJ, Ackerson BK, Sy LS, et al. Observational safety study of febrile convulsion following first dose MMRV vaccination in a managed care setting. Vaccine 2009;27:4656–61.
§ Statistically significant at <0.05.

among every 2,600 children vaccinated with a first dose of MMRV vaccine compared with children vaccinated with a first dose of MMR vaccine and varicella vaccine administered at the same visit. During 0–30 days postvaccination, the rate of febrile seizure was 14 per 10,000 vaccinations among MMRV vaccine recipients and 13 per 10,000 vaccinations among MMR vaccine and varicella vaccine recipients; the RR was 1.1 (CI = 0.7–1.7; p=0.66).

The CDC-sponsored study was conducted through the Vaccine Safety Datalink (VSD),* a collaboration between CDC and eight MCOs that routinely monitors vaccine safety of new vaccines by near real-time surveillance (*16*). Each MCO site prepares data files containing demographic and medical information on their members and ICD-9 codes assigned to medical encounters. Surveillance conducted through VSD assesses the risk for prespecified health outcomes during prespecified periods after vaccination; the 42-day interval postvaccination is used commonly to study a variety of vaccine adverse events. VSD monitoring of MMRV vaccine detected an increased risk for seizure of any etiology in the interval of 42 days postvaccination among children aged 12–23 months after administration of first dose of MMRV vaccine compared with administration of first dose of MMR vaccine (many children also received varicella vaccine) (*17*). When children who received MMRV vaccine were compared with children who received MMR vaccine and varicella vaccine administered at the same visit, statistically significant clustering of seizures of any etiology was observed 7–10 days after vaccination in both groups, with more seizures observed among children who had received MMRV vaccine (p=0.0001) (*18*).

To further evaluate this finding, VSD initiated a cohort study to determine the risk for febrile seizures 7–10 days and 0–42 days postvaccination among 83,107 children aged 12–23 months who received the first dose of MMRV vaccine during January 2006–October 2008 and a cohort of 376,354 children aged 12–23 months who received the first dose of MMR vaccine and varicella vaccine administered at the same visit during January 2000–October 2008. Investigators reviewed medical records of study children to identify those with a clinical diagnosis of febrile seizure within 42 days after vaccination as defined by ICD-9 codes for seizures (345X [epilepsy] and 780.3X [convulsion]). Poisson regression was used to adjust for age, respiratory season, and other covariates. During 7–10 days after vaccination, the unadjusted rate of febrile seizures was 8.5 per 10,000 vaccinations among MMRV vaccine recipients and 4.2 per 10,000 vaccinations among those who received MMR vaccine and varicella vaccine at the same visit (adjusted RR: 2.0; CI = 1.4–2.9; p = 0.0001) (Table). These results suggest that, during the 7–10 day postvaccination period, approximately one additional febrile seizure occurred among every 2,300 children vaccinated with a first dose of MMRV vaccine compared with children vaccinated with a first dose of MMR vaccine and varicella vaccine administered at the same visit. During 0–42 days postvaccination, the RR was 1.5 (CI = 1.1–1.9; p<0.05). An additional VSD analysis of the febrile seizure risk during 0–30 days postvaccination, (the interval used in the Merck-sponsored study) yielded similar findings as those for the 0–42 days postvaccination interval (*18*).

Risk for Febrile Seizure After Second Dose of MMRV Vaccine

Rates for febrile seizures are lower among children aged 4–6 years (the recommended age for the second dose of MMRV vaccine, MMR vaccine, and varicella vaccine) than among children aged 12–15 months (*14*). In prelicensure studies conducted among children who received their second dose in their second year of life and 3 months after their first dose, the second dose of MMRV vaccine was less likely to cause fever

* Additional information is available at http://www.cdc.gov/od/science/iso/vsd.

than the first dose (*12,13*). Among children aged 4–6 years who received MMRV vaccine for their second dose, the rate of fever was similar to the rate following a second dose of MMR vaccine and varicella vaccine at the same visit (*19*).

Assessing the risk for febrile seizures after the second dose vaccination was not an initial objective of either postlicensure study. In light of findings from first-dose studies, the workgroup requested available data on febrile seizures risk after the second dose from both VSD and Merck. In the data that VSD provided in response to this request, the febrile seizure risk after the second dose was inferred from data among children aged 4–6 years, which is the age when the second dose is routinely recommended. In the data provided by Merck, second-dose subjects were children aged 1–12 years (>95% were aged 4–6 years) who had received MMR vaccine previously, with or without varicella vaccine (for most children in the MMR vaccine and varicella vaccine group, only a second dose of MMR vaccine was administered) (*20*). During 7–10 days following vaccination, the VSD study identified one febrile seizure among 84,653 children aged 4–6 years who received MMRV vaccine and no febrile seizures among 64,663 children the same age who received MMR vaccine and varicella vaccine administered at the same visit (*17*). No febrile seizures occurred during the 5–12 days postvaccination in either group in the Merck-sponsored study (25,212 children received a second dose of MMRV vaccine, and 24,788 received a second dose of MMR vaccine and varicella vaccine at the same visit) (*20*). Therefore, among children aged 4–6 years, postlicensure data do not suggest that children who received MMRV vaccine as a second dose had an increased risk for febrile seizures after vaccination compared with children who received a second dose of MMR vaccine and varicella vaccine at the same visit.

Clinical Importance of Febrile Seizure

Febrile seizures occur most commonly with the fevers caused by typical childhood illnesses (e.g., middle-ear infections, viral upper respiratory tract infections, and roseola) but can be associated with any condition that results in fever, including vaccination. MMR vaccine is associated with an increased risk for febrile seizures occurring 8–14 days after vaccination among children aged <7 years, resulting in an estimated one additional febrile seizure among every 3,000–4,000 children vaccinated with MMR vaccine compared with children not vaccinated during the preceding 30 days (*8*). Studies have not demonstrated an increased risk for febrile seizures during the 30-day period following varicella vaccination, after controlling for the simultaneous administration of MMR vaccine (*21*).

By age 5 years, approximately one in every 25 children will have had a febrile seizure. Febrile seizures usually occur among children aged 6–59 months; the peak age is 14–18 months (*14*), and approximately 97% of febrile seizures occur in children aged <4 years (*22*). Approximately one third of children with a first febrile seizure will have recurrent febrile seizures (*23*). Parents and caregivers of children who have a first febrile seizure are likely to seek medical attention, which commonly includes a visit to an emergency department.

The prognosis for young children who have febrile seizures generally is excellent (*14*). The majority (>90%) of children who have a febrile seizure will not develop epilepsy; certain factors (e.g., presence of complex features during the seizure [duration of seizure >15 minutes, occurrence of more than a single seizure within 24 hours, and focal features], an initial febrile seizure before age 12 months, delayed developmental milestones, or a pre-existing neurologic disorder) and genetic predisposition (i.e., family history of epilepsy) are associated with future development of epilepsy after a febrile seizure (*14,23*). Children who have a febrile seizure soon after MMR vaccination (within 2 weeks or within 7–21 days, depending on the study) are not more likely to have future epilepsy or neurodevelopment disorders than children who have febrile seizures for other reasons (*8,10*). However, one study indicated that these children might have a slightly higher risk for having another febrile seizure than children who had a febrile seizure for other reasons (RR = 1.19; CI = 1.01–1.41) (*10*). Although data on sequelae of febrile seizures after MMRV vaccine are not available, the findings described for MMR vaccine likely also are applicable to MMRV vaccine.

When a child experiences a febrile seizure, negative effects on family members or caregivers can result, including adverse mental and physical health consequences (*24–27*). Parents and caregivers generally consider febrile seizures to be a more severe adverse event than physicians (*28,29*).

Measles, Mumps, Rubella, and Varicella Disease Burden

The burden of disease for measles, mumps, rubella, and varicella in the United States is very low. Endemic transmission for measles and rubella was declared eliminated in 2000 and 2004, respectively (*30,31*). For mumps, the average reported incidence has been 0.1 per 100,000 population since 1993, except in 2006, when a large outbreak occurred primarily affecting the Midwest (*32*), and during 2009–2010, when an outbreak occurred in a religious community in the Northeast (*33*). During 1995–2005, reported varicella incidence declined approximately 90% (*34*). The very low levels of disease are attributed to high population immunity achieved through the use of MMR vaccine and varicella vaccine. After the elimination of measles was achieved, a number of outbreaks of limited size occurred as a result of importation into primarily

unvaccinated populations; these outbreaks did not extend to the highly 2-dose vaccinated populations (*35*).

Immunogenicity and Efficacy of MMRV Vaccine

MMRV vaccine was licensed on the basis of noninferior immunogenicity of the antigenic components compared with simultaneous administration of MMR vaccine and varicella vaccine (*36*). Formal studies to evaluate the clinical efficacy of MMRV vaccine have not been performed; efficacy of MMRV vaccine was inferred from that of MMR vaccine and varicella vaccine on the basis of noninferior immunogenicity.

Programmatic Considerations

Vaccine Coverage

Among children aged 19–35 months, vaccine coverage with ≥1dose of MMR vaccine and varicella vaccine is high; since 1996, coverage with MMR vaccine has been 90%–93%, and in 2008, coverage with varicella vaccine reached 91%. In 2008, coverage with ≥1 dose of MMR vaccine by state ranged from 85.9% to 95.6%; coverage with ≥1 dose of varicella vaccine by state ranged from 77.0% to 95.3% (*37*). For school-aged children, school-entry requirements have proved to be an effective strategy for achieving and maintaining high vaccine coverage (*38*). All states have school-entry requirements for 2 doses of MMR vaccine, and 46 states have school-entry requirements for 1 dose of varicella vaccine. As of September 2009, a total of 22 states had school-entry requirements for 2 doses of varicella vaccine (CDC, unpublished data, 2009). No data were available on the rate of coverage for 2 doses of varicella vaccine.

Maintaining high vaccination coverage is important for disease control. Combination vaccines reduce the number of injections children receive and have the potential to improve vaccination coverage and timeliness of vaccination. However, evidence is limited about the impact of the use of newer combination vaccines on vaccination coverage. Two studies suggested that receipt of *Haemophilus influenzae* type b (Hib)–hepatitis B (HepB) or pediatric diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP)-HepB–inactivated poliovirus vaccine (IPV) combination vaccines was associated with 3%–6% increased coverage for DTaP, IPV, Hib, HepB vaccines compared with the coverage among children who did not receive the combination vaccines (*39,40*). Another study did not find increased coverage for the component vaccines when combination Hib-HepB was used, probably because the coverage rates were already high before introduction of the combination vaccine (*41*). No published literature has specifically assessed the impact of MMRV vaccine on coverage for varicella or other vaccines recommended at age 12–15 months. However, several studies have indicated parent and provider preference for fewer injections at one visit (*42–44*).

Physicians' and Parents' Attitudes on Use of MMRV Vaccine

To better understand attitudes toward use of MMRV vaccine in light of postlicensure findings on febrile seizure risk after the first dose of MMRV vaccine, CDC sponsored a physician survey in 2008 and two parent focus groups in 2009. The physician survey included a nationally representative sample of pediatricians and family physicians (*29,45*). The response rate was 76% for pediatricians (321 of 425) and 71% for family physicians (299 of 424). After being provided with a summary of the findings from the two postlicensure studies of febrile seizure after MMRV vaccination, 59% of pediatricians and 67% of family physicians responded that they would either definitely or probably recommend MMR vaccine and varicella vaccine for the first-dose vaccination for a child aged 12–15 months; 21% and 9%, respectively, would definitely or probably recommend MMRV vaccine; and 20% and 24%, respectively, said they would let the parents decide.[†]

The parent focus groups were conducted in two cities (Kirkland, Washington, and New York City, New York) (*28*). A total of 82 mothers of children aged 7 months–3 years were selected, all of whom reported that they expected their children to receive all or most of the recommended childhood vaccines. Mothers were presented with background materials on febrile seizure risk after the first dose of MMRV vaccine compared with the first dose of MMR vaccine and varicella vaccine. After reviewing and discussing the risks and benefits of both vaccination options, mothers were asked whether they would accept MMRV vaccine for the first-dose vaccination if their pediatrician recommended it; 41% said they would accept vaccination with MMRV vaccine, and 31% said they would refuse. Trust in their pediatrician's judgment was a major factor for mothers' acceptance of MMRV vaccine for their children. Mothers who reported that they would refuse MMRV vaccine said they were unwilling to accept any additional risk over that of MMR vaccine and varicella vaccine, regardless of how small.

[†] Based on response to the following question: "Assuming that your practice has adequate supplies of MMRV, MMR, and varicella vaccines to administer to all your patients, which vaccine(s) would you recommend to a healthy 12–15 month old child?" Answer options were as follows: "1) definitely recommend MMRV, 2) probably recommend MMRV, 3) would let parents choose between MMRV and separate MMR and varicella, 4) probably recommend separate MMR and varicella, and 5) definitely recommend separate MMR and varicella."

Summary and Rationale for MMRV Vaccine Recommendations

Two postlicensure studies (*11,18*) and other related data support the conclusion that use of MMRV vaccine among children aged 12–23 months results in a higher risk for fever and febrile seizures during the 5–12 days after the first dose compared with the use of MMR vaccine and varicella vaccine at the same visit. The approximately twofold increased risk results in an estimated one additional febrile seizure per 2,300–2,600 children vaccinated with the first dose of MMRV vaccine compared with those who receive the first dose with MMR vaccine and varicella vaccine. Although data regarding the risk for febrile seizures after administration of the first dose of MMRV vaccine are available only for children aged 12–23 months, the increased risk for febrile seizures during the 5–12 days postvaccination is likely to be present among children aged ≤47 months because that is the biologic window of vulnerability for febrile seizures in children (approximately 97% of febrile seizures occur in children aged <4 years) (*22*). Compared with no vaccination, MMR vaccine is associated with one additional febrile seizure among every 3,000–4,000 children aged <7 years vaccinated with MMR vaccine (*8*). The risk for febrile seizures during measles illness is higher than the risk after either MMRV vaccine or MMR vaccine (between one in 40 and one in 1,000 children with measles experience a febrile seizure) (*46*).

Results from postlicensure studies do not suggest that children aged 4–6 years who receive the second dose of MMRV vaccine have an increased risk for febrile seizures after vaccination compared with children the same age who receive the second dose of MMR vaccine and varicella vaccine at the same visit (*11,17*). Prelicensure data indicated that the rate of fever after the second dose of MMRV administered to children aged 15–26 months was lower than after the first dose administered to children the same age as either MMRV vaccine or MMR vaccine and varicella vaccine at the same visit (*12*).

The evidence suggests that the two vaccine options (MMRV vaccine or MMR vaccine and varicella vaccine) are equivalent in terms of efficacy, effectiveness, immunogenicity, and burden of disease prevented with the first dose. Evidence to date is not sufficient to demonstrate a clear advantage of either option for the first dose in terms of an impact on program implementation. For the second dose, routine use of MMRV vaccine has the potential to increase second-dose varicella vaccine coverage and thus have a greater impact on controlling varicella disease than MMR vaccine and varicella vaccine, particularly in states that lack school-entry requirements for a second dose of varicella vaccine.

Although a vaccination strategy that would result in the fewest adverse events might be preferred, maximizing choice based on parent or caregiver and physician preference also is an important ethical principle. The decision-making process must include provision of specific information to parents and caregivers about the risk for febrile seizures associated with receipt of the first dose of MMRV vaccine compared with the first dose of MMR vaccine and varicella vaccine.

Use of MMRV vaccine has the benefit of requiring one less injection than the alternative of MMR vaccine and varicella vaccine. The risk for a febrile seizure after the first dose of MMRV vaccine, although low, is higher than after MMR vaccine and varicella vaccine administered as separate injections, and use of MMR vaccine and varicella vaccine avoids this increased risk. Children who have febrile seizures generally have an excellent prognosis. However, first febrile seizures often require a medical visit to an emergency department and are distressing for parents and caregivers. Therefore, parents might prefer to avoid the small increased risk for fever and febrile seizures after the first dose of MMRV vaccine compared with the first dose of MMR vaccine and varicella vaccine administered as separate injections. Given the balance of risks and benefits of a first dose of MMRV vaccine compared with a first dose of MMR vaccine and varicella vaccine, and the importance of individual values and preferences in weighing these risks and benefits, decisions should be made by providers and parents or caregivers on a case-by-case basis.

Recommendations for Use of MMRV Vaccine

ACIP recommendations for use of MMRV vaccine have been summarized (Box). The routinely recommended ages for measles, mumps, rubella, and varicella vaccination continue to be 12–15 months for the first dose and 4–6 years for the second dose.

MMRV vaccine may be administered simultaneously with other vaccines recommended for children aged 12–15 months and 4–6 years. If simultaneous administration is not possible, MMRV vaccine may be administered at any time before or after an inactivated vaccine but at least 28 days before or after another live, attenuated vaccine, except varicella vaccine, for which a minimum interval of 3 months is recommended. Guidance on administration of MMRV vaccine in special situations (e.g., administration of antibody-containing products or tuberculosis screening and skin test reactivity) has been published previously (*47*).

BOX. Summary of recommendations for measles, mumps, rubella and varicella (MMRV) vaccine use

- The routinely recommended ages for measles, mumps, rubella and varicella vaccination continue to be age 12–15 months for the first dose and age 4–6 years for the second dose.
- For the first dose of measles, mumps, rubella, and varicella vaccines at age 12–47 months, either measles, mumps, and rubella (MMR) vaccine and varicella vaccine or MMRV vaccine may be used. Providers who are considering administering MMRV vaccine should discuss the benefits and risks of both vaccination options with the parents or caregivers. Unless the parent or caregiver expresses a preference for MMRV vaccine, CDC recommends that MMR vaccine and varicella vaccine should be administered for the first dose in this age group.
- For the second dose of measles, mumps, rubella, and varicella vaccines at any age (15 months–12 years) and for the first dose at age ≥48 months, use of MMRV vaccine generally is preferred over separate injections of its equivalent component vaccines (i.e., MMR vaccine and varicella vaccine). Considerations should include provider assessment, patient preference, and the potential for adverse events.
- A personal or family (i.e., sibling or parent) history of seizures of any etiology is a precaution for MMRV vaccination. Children with a personal or family history of seizures of any etiology generally should be vaccinated with MMR vaccine and varicella vaccine.

First Dose at Age 12–47 Months

The routinely recommended age for the first dose of measles, mumps, rubella, and varicella vaccines is age 12–15 months; children not vaccinated according to the routine schedule may receive the first dose of MMRV vaccine up to age 12 years. For the first dose of measles, mumps, rubella, and varicella vaccines at age 12–47 months, either MMR vaccine and varicella vaccine or MMRV vaccine may be used. Providers who are considering administering MMRV vaccine should discuss the benefits and risks of both vaccination options with the parents or caregivers. Unless the parent or caregiver expresses a preference for MMRV vaccine, CDC recommends that MMR vaccine and varicella vaccine should be administered for the first dose in this age group.

The discussion with parents or caregivers should focus on helping them understand the risks and benefits using tools including the Vaccine Information Statements. Compared with use of MMR vaccine and varicella vaccine at the same visit, use of MMRV vaccine results in one fewer injection but is associated with a higher risk for fever and febrile seizures 5–12 days after the first dose among children aged 12–23 months (approximately one extra febrile seizure for every 2,300–2,600 MMRV vaccine doses). Use of MMR vaccine and varicella vaccine avoids this increased risk for fever and febrile seizures following MMRV vaccine.

The 47-month cutoff was selected on the basis of the epidemiology of febrile seizures. Approximately 97% of febrile seizures occur in children aged ≤47 months.

Second Dose at Any Age and First Dose at Age ≥48 Months

Although the routinely recommended age for the second dose of measles, mumps, rubella, and varicella vaccines is 4–6 years, the second dose may be administered before age 4 years, provided ≥3 months have elapsed since the first dose. MMRV vaccine is licensed for use among children through age 12 years. For the second dose of measles, mumps, rubella, and varicella vaccines at any age (15 months–12 years) and for the first dose at age ≥48 months, use of MMRV vaccine generally is preferred over separate injections of its equivalent component vaccines (i.e., MMR vaccine and varicella vaccine). Considerations should include provider assessment (i.e., the number of injections, vaccine availability, likelihood of improved coverage, likelihood of patient return, and storage and cost considerations), patient preference, and the potential for adverse events. This recommendation is consistent with ACIP's 2009 provisional general recommendations on combination vaccines (*48*).

Other MMRV Vaccine-Related Guidance

New Precaution for MMRV Vaccine Use

A personal or family (i.e., sibling or parent) history of seizures of any etiology is a precaution[§] for MMRV vaccination. Studies suggest that children who have a personal or family history of febrile seizures or family history of epilepsy are at increased risk for febrile seizures compared with children without such histories (*10,49*). Children with a personal or family history of seizures of any etiology generally should be vaccinated with MMR vaccine and varicella vaccine because the risks for using MMRV vaccine in this group of children generally outweigh the benefits.

Contraindications and Precautions for MMRV Vaccine Use

Contraindications for use of MMRV vaccine include

- history of anaphylactic reaction to neomycin;
- allergic reaction to gelatin, other component of the vaccine, or after previous vaccination with MMRV vaccine, varicella vaccine or MMR vaccine;
- altered immunity (i.e., blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic system);
- primary or acquired immunodeficiency including HIV infections/AIDS, cellular immune deficiencies, hypogammaglobulinemia, and dysgammaglobulinemia;
- family history of congenital or hereditary immunodeficiencies, unless the immune competence of the potential vaccine recipient has been demonstrated;
- systemic immunosuppressive therapy, including oral steroids ≥2 mg/kg of body weight or ≥20 mg/day of prednisone or equivalent for persons who weigh >10 kg, when administered for ≥2 weeks); and
- pregnancy.

Precautions for use of MMRV vaccine include

- recent (≤11 months) receipt of antibody-containing blood product (specific interval depends on dose administered);
- history of thrombocytopenia or thrombocytopenic purpura;
- moderate or severe acute illness with or without fever; and
- a personal or family (i.e., sibling or parent) history of seizures of any etiology.

Use of Antipyretics for Prevention of Febrile Seizures

Studies have not demonstrated that antipyretics (e.g., acetaminophen or ibuprofen) prevent febrile seizures (*50*). Vaccination with either MMR vaccine or MMRV vaccine can cause fever and, rarely, febrile seizures. Most fevers and febrile seizures after administration of a measles-containing vaccine occur 5–12 days after vaccination with the first dose. Parents and caregivers should be counseled about the possibility of fever after receipt of a measles-containing vaccine and educated on timing and measures to control it. Guidance on diagnosis and management of febrile seizures has been published previously (*14,50*).

Reporting of Adverse Events after Vaccination

Clinically significant adverse events that follow vaccination should be reported to the Vaccine Adverse Event Reporting System (VAERS) at http://vaers.hhs.gov/esub/index. Reports can be filed securely online, by mail, or by fax. A VAERS form can be downloaded from the VAERS website or requested by sending an e-mail message to info@vaers.org, by calling telephone 1-800-822-7967, or by sending a faxed request to 1-877-721-0366. Additional information on VAERS or vaccine safety is available at http://vaers.hhs.gov/about/index or by calling telephone 1-800-822-7967.

National Vaccine Injury Compensation Program

The National Vaccine Injury Compensation Program (VICP), established by the National Childhood Vaccine Injury Act of 1986 (as amended), provides a mechanism through which compensation can be paid on behalf of a person determined to have been injured or to have died as a result of receiving a vaccine covered by VICP. The Vaccine Injury Table lists the vaccines covered by VICP and the injuries and conditions (including death) for which compensation might be paid. If the injury or condition is not on the table, or does not occur within the specified time period on the table, persons must prove that the vaccine caused the injury or condition.

Persons of all ages who receive a VICP-covered vaccine might be eligible to file a claim. MMRV vaccine, MMR vaccine and varicella vaccine are covered under VICP.

[§] A precaution is a condition in a recipient that might increase the risk for a serious adverse reaction or that might compromise the ability of the vaccine to produce immunity (e.g., administering measles vaccine to a person with passive immunity to measles from a blood transfusion). A person might experience a more severe reaction to the vaccine than would have otherwise been expected; however, the risk for this happening is less than expected with a contraindication. In general, vaccinations should be deferred when a precaution is present. However, a vaccination might be indicated in the presence of a precaution because the benefit of protection from the vaccine outweighs the risk for an adverse reaction. (CDC. ACIP general recommendations on immunization. MMWR 2006;55[No. RR-15]).

Additional information about VICP is available at http://www.hrsa.gov/vaccinecompensation or by calling telephone 1-800-338-2382.

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