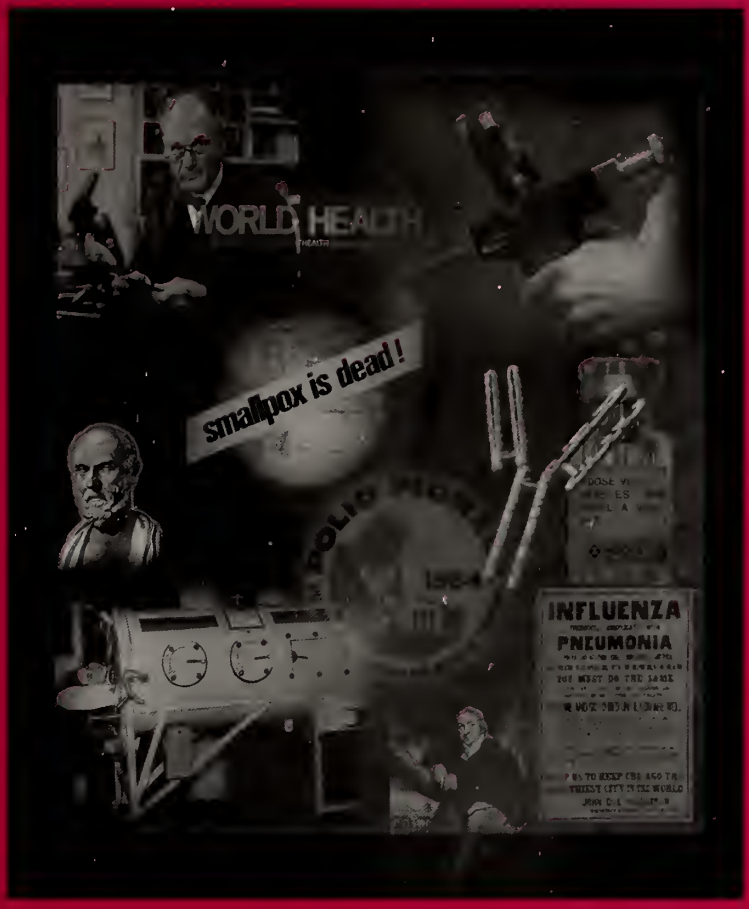
Epidemiology and Prevention *of* Vaccine-Preventable Diseases



9th EDITION

JANUARY 2006

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

Epidemiology and Prevention
of
Vaccine-Preventable Diseases

9th EDITION

JANUARY 2006

Edited by: William Atkinson, MD, MPH
Jennifer Hamborsky, MPH, CHES
Lynne McIntyre, MALS
Charles (Skip) Wolfe

Layout and Design: Susie P. Childrey

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

On the Cover

A montage of images from the history of immunization. Clockwise from upper left: **John Enders**, who with his colleagues Thomas Weller and Fred Robbins first grew poliovirus in human cell culture in 1948; the May 1980 edition of **World Health magazine** announcing the eradication of smallpox; a vaccine **jet injector**, developed in 1967; a **molecule of immunoglobulin type G** (IgG), a critical component of the receptor theory of immunity developed by Paul Ehrlich in 1897; **MMR vaccine**, first licensed in 1971; an **influenza warning poster** developed by the Chicago Public Health Department in 1918; **Edward Jenner**, who developed the first vaccine (smallpox) in 1796; a **Polio Pioneer button**, given to the children who volunteered for the Francis Field Trial of poliovirus vaccine in 1954; a **Drinker respirator** (iron lung), which saved the lives of thousands of people paralyzed by polio in the 1940s and 1950s; and **Hippocrates**, a Greek physician who described diphtheria, epidemic jaundice (probably hepatitis A), and other diseases in the 5th century BCE. He was said to have originated the medical maxim *primum non nocere*—first, do no harm.

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Milestones in the History of Vaccination

400BCE
Hippocrates describes diphtheria, epidemic jaundice, and other conditions

1100s
Variolation for smallpox first reported in China

1721
Variolation introduced into Great Britain

1796
Edward Jenner inoculates James Phipps with cowpox, and calls the procedure vaccination ("vacca" is Latin for cow).

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Milestones in the History of Vaccination

1870 Louis Pasteur creates the first live attenuated bacterial vaccine (chicken cholera)

1884 Pasteur creates the first live attenuated viral vaccine (rabies)

1885 Pasteur first uses rabies vaccine in a human

1887 Institut Pasteur established

1900 Paul Ehrlich formulates receptor theory of immunity

Milestones in the History of Vaccination

1901
First Nobel Prize in Medicine to von Behring for diphtheria antitoxin

1909
Theobald Smith discovers a method for inactivating diphtheria toxin

1919
Calmette and Guerin create BCG, the first live attenuated bacterial vaccine for humans

1923
First whole-cell pertussis vaccine tested
Gaston Ramon develops diphtheria toxoid

1926
Ramon and Christian Zoeller develop tetanus toxoid

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Milestones in the History of Vaccination

1927 Yellow fever virus isolated

1931 Goodpasture describes a technique for viral culture in hens' eggs

1936 Thomas Francis and Thomas Magill develop the first inactivated influenza vaccine

1948 John Enders and colleagues isolate Lansing Type II poliovirus in human cell line

1954 Enders and Peebles isolate measles virus Francis Field Trial of inactivated polio vaccine

Milestones in the History of Vaccination

1955
Inactivated polio vaccine licensed

1961
Human diploid cell line developed

1963
Measles vaccine licensed
Trivalent oral polio vaccine licensed

1965
Bifurcated needle for smallpox vaccine licensed

1966
World Health Assembly calls for global smallpox eradication

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Milestones in the History of Vaccination

1967	1969	1971	1977	1979
Maurice Hilleman develops Jeryl Lynn strain of mumps virus	Stanley Plotkin develops RA23/7 strain of rubella virus	MMR vaccine licensed	Last indigenous case of smallpox (Somalia)	Last wild poliovirus transmission in the U.S.

Milestones in the History of Vaccination

1981	1983	1986	1989	1990
First hepatitis B vaccine licensed	Smallpox vaccine withdrawn from civilian market	First recombinant vaccine licensed (hepatitis B) National Childhood Vaccine Injury Act	Two-dose measles vaccine recommendation	First polysaccharide conjugate vaccine licensed (*Haemophilus influenzae* type b)

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Milestones in the History of Vaccination

1994	1995	1996	1997	1998
Polio elimination certified in the Americas Vaccines for Children program begins	Varicella vaccine licensed Hepatitis A vaccine licensed First harmonized childhood immunization schedule published	Acellular pertussis vaccine licensed for infants	Sequential polio vaccination recommended	First rotavirus vaccine licensed

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Milestones in the History of Vaccination

1999
clusive use of inactivated
lio vaccine recommended
tavirus vaccine withdrawn

2000
Pneumococcal conjugate vaccine licensed for infants

2003
Live attenuated influenza vaccine licensed

2004
Inactivated influenza vaccine recommended for all children 6–23 months of age

2005
Acellular pertussis vaccines licensed for adolescents and adults
MMR licensed

Vaccines and Related Products Distributed in the United States

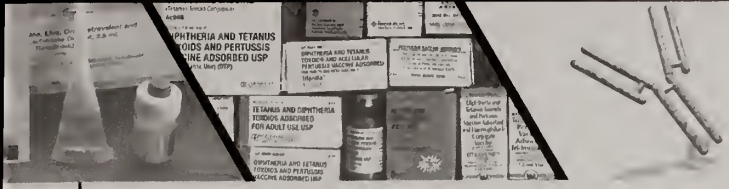
This product listing is current as of October 2005.

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 (DT; ped <7yrs, P-free)	generic	sanofi pasteur	Inactivated	single-dose vial
Tetanus, diphtheria, adsorbed (Td; ≥7 yrs, P-free)	Decavac	sanofi pasteur	Inactivated	single-dose syringe
Tetanus, diphtheria, adsorbed (Td; ≥7 yrs)	generic	Mass. Biologic Labs[1]	Inactivated	15-dose vial
Tetanus, diphtheria, acellular Pertussis (Tdap; 10–18 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
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)	Fluvirin	Chiron	Inactivated	single-dose syringe and 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)
Measles, Mumps, Rubella (MMR)	M-M-R II	Merck	Live attenuated	single-dose vial
Measles	Attenuvax	Merck	Live attenuated	single-dose vial
Mumps	Mumpsvax	Merck	Live attenuated	single-dose vial
Rubella	Meruvax 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 and 10-dose vial
Varicella	Varivax	Merck	Live attenuated	single-dose vial
Varicella-zoster immune globulin (VZIG)	generic	Mass. Biologic Labs[2]	Human immunoglobulin	125-unit and 625-unit vials
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	Chiron	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

[1]Distributed by General Injectables and Vaccines (800) 521-7468
[2]Distributed by FFF Enterprises (800) 843-7477

Vaccine Company Contact Information

Berna Products Corporation (www.bernaproducts.com) ..... (800) 533-5899
BioPort Corporation (www.bioport.com) ..... (877) 246-8472
Chiron Corporation (www.chiron.com & www.rabavert.com) ..... (800) 244-7668
GlaxoSmithKline (www.gskvaccines.com) ..... (866) 475-8222
MedImmune Vaccines, Inc. (www.medimmune.com) ..... (877) 633-4411
Merck & Co., Inc. (www.merckvaccines.com) ..... (800) 637-2579
Nabi Biopharmaceuticals (www.nabi.com) ..... (800) 327-7106
sanofi pasteur (www.us.sanofipasteur.com) ..... (800) 822-2463
Talecris Biotherapeutics (www.talecris.com) ..... (800) 243-4153
Wyeth Vaccines (www.wyeth.com) ..... (800) 572-8221



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 very specific to a single organism or group of closely related organisms. There are two basic mechanisms for acquiring immunity, active and passive.

Principles of Vaccination

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

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.

Principles of Vaccination

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

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

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, called **antibodies** (or immunoglobulins), and of specific cells (also known as **cell-mediated immunity**) whose purpose is to facilitate the elimination of foreign substances.

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

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.

Passive Immunity

- Transfer of antibody produced by one human or other animal to another
- Temporary protection
- Transplacental most important source in infancy

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).

Sources of Passive Immunity

- Almost all blood or blood products
- Homologous pooled human antibody (immune globulin)
- Homologous human hyperimmune globulin
- Heterologous hyperimmune serum (antitoxin)

Virtually all 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.

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, a 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 cell, 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

Two globulin products are available for the prevention or treatment of respiratory syncytial virus (RSV) infection: RSV-IGIV and palivizumab (**Synagis**). RSV-IGIV is a hyperimmune globulin from human donors. It contains antibody other than RSV, like other hyperimmune globulin products. Palivizumab is a humanized monoclonal antibody specific for RSV. It does not contain any other antibody except RSV antibody.

Antibody for Prevention of RSV

- RSV-IGIV
  - human hyperimmune globulin
  - contains other antibodies
- Palivizumab (Synagis)
  - monoclonal
  - contains only RSV antibody

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 have the natural disease. 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. Vaccines 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 adjuvants (e.g., aluminum-containing materials 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.

Classification of Vaccines

- Live attenuated
  - viral
  - bacterial
- Inactivated

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, two live attenuated bacterial vaccines are also available.

Inactivated Vaccines

Whole
- viruses
- bacteria

Fractional
- protein-based
  - toxoid
  - subunit
- polysaccharide-based
  - pure
  - conjugate

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 are those in which the polysaccharide 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

- Attenuated (weakened) form of the "wild" virus or bacterium
- Must replicate to be effective
- Immune response similar to natural infection
- Usually effective with one dose*

*except those administered orally

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 vaccine used 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 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 are **usually effective with one dose, except those administered orally.**

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 growth 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, yellow fever, and influenza (intranasal). Oral polio vaccine is a live viral vaccine but is no longer available in the United States. A new live recombinant rotavirus vaccine may be licensed in the future. Live attenuated bacterial vaccines are bacille Calmette-Guérin (BCG) 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, yellow fever, intranasal influenza, (oral polio) (rotavirus)
• Bacterial	BCG, oral typhoid

Vaccines in (parenthesis) are not available in the United States.

Inactivated Vaccines

- Cannot replicate
- Less interference from circulating antibody than live vaccines
- Generally require 3-5 doses
- Immune response mostly humoral
- Antibody titer diminishes with time

Inactivated Vaccines

Whole-cell vaccines

• Viral	polio, hepatitis A, rabies (influenza)
• Bacterial	(pertussis) (typhoid) (cholera) (plague)

Vaccines in (parenthesis) are not available in the United States.

Inactivated Vaccines

Fractional vaccines

• Subunit	hepatitis B, influenza, acellular pertussis, (Lyme) (HPV)
• Toxoid	diphtheria, tetanus

Vaccines in (parenthesis) are not available in the United States.

Polysaccharide Vaccines

Pure polysaccharide
- pneumococcal
- meningococcal
- *Salmonella* Typhi (Vi)

Conjugate polysaccharide
- *Haemophilus influenzae* type b
- pneumococcal
- meningococcal

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. Inactivated vaccines 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, rabies, and hepatitis A). 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) and toxoids (diphtheria, tetanus). A subunit vaccine for Lyme disease is no longer available in the United States. A vaccine containing the capsid protein (L1) of human papillomavirus may be available in the future.

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 is not seen with polysaccharide antigens; repeat doses of polysaccharide vaccines 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 <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. Three genetically engineered vaccines are currently available in the United States. Hepatitis B vaccines are produced by insertion of a segment of the hepatitis B virus gene into the gene of a yeast cell. The modified yeast cell produces pure hepatitis B surface antigen 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.

Selected References

Ada G. The immunology of vaccination. In: Plotkin SA, Orenstein WA. *Vaccines*. 4th ed. Philadelphia, PA: Saunders, 2003:31–45.

General Recommendations on Immunization

This chapter discusses issues that are commonly encountered in vaccination practices. 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 and the American Academy of Family Physicians. These recommendations are revised every 3–5 years as needed; the most current edition was published in February 2002 (*MMWR* 2002;51(RR–2):1–36). A revised document is expected to be published in 2006. All providers who administer vaccine should have a copy of this report and be familiar with its contents. 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 vaccine), simultaneous and nonsimultaneous administration of different vaccines, and the interval between subsequent doses of the same vaccine.

Issues Regarding Timing and Spacing of Vaccines

- Timing of antibody-containing blood products and live vaccines
- Simultaneous and nonsimultaneous administration of different vaccines
- 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 substantially 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 Live Vaccines

Product Given First	Action
Vaccine	Wait 2 weeks before giving antibody
Antibody	Wait >3 months before giving vaccine (See Table, Appendix A)

Live vaccines must replicate in order to cause an immune response. Antibody against parenteral (injected) live vaccine antigen may interfere with replication. If a live parenteral vaccine (measles-mumps-rubella [MMR] or varicella) 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 vaccine depends on the concentration of antibody in the product. A table listing the recommended intervals between administration of antibody products and live vaccines (MMR and varicella) is included in Appendix A and in the General Recommendations on Immunization. The interval between administration of an antibody product and MMR or varicella vaccination can be as long as 11 months.

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. Because of the importance of rubella immunity among childbearing age women, postpartum vaccination of rubella-susceptible women with rubella or MMR 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 months later to ensure immunity to rubella and, if necessary, to measles.

Oral typhoid, and yellow fever vaccines are not affected by the administration of immune globulin or blood products. They may be given simultaneously with blood products, or separated by any interval. These vaccines are not affected 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. The effect of circulating antibody on live attenuated influenza vaccine is not known.

Two antibody products are available for the prevention of respiratory syncytial virus (RSV) infection in infants and young children. RSV-IG (RespiGam) is an intravenous

Antibody for Prevention of RSV

- RSV-IG (RespiGam)
  - —Human
  - —Contains other antibodies
- Palivizumab (Synagis)
  - —Monoclonal
  - —Contains only RSV antibody

human immune globulin product. RSV-IG contains other human antibodies in addition to antibody to RSV, and may interfere with live parenteral vaccines for as long as 9 months. Palivizumab (Synagis) contains only monoclonal antibody to respiratory syncytial virus (RSV). It does not interfere with the response to live virus vaccines.

General Rule

There is no contraindication to the simultaneous administration of any vaccines.

Simultaneous and Nonsimultaneous Administration

Simultaneous administration of the most widely used live and inactivated vaccines does not result in decreased antibody responses or increased rates of adverse reactions.

Simultaneous administration of all vaccines for which a child is eligible can be 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.

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 Hib/DTaP (TriHIBit) vaccine is licensed for mixing in the same syringe.

Nonsimultaneous Administration of Different Vaccines

In some situations, vaccines that could be given simultaneously are not (e.g., if the child is receiving vaccines from two different providers). **Live parenteral (injected) vaccines (MMR, varicella, and yellow fever) and live attenuated influenza vaccine (LAIV) that are not administered simultaneously should be separated by at least 4 weeks.** This precaution 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 simultaneously but are separated by less than 4 weeks, the vaccine given second should be repeated in 4 weeks or confirmed to be effective by serologic testing of the recipient (serologic testing is not recommended for LAIV). An exception to this recommendation is yellow fever vaccine

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 <4 weeks apart the vaccine given second should be repeated
- Exception is yellow fever vaccine given <4 weeks after measles 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, and yellow fever vaccines is not known.

Live vaccines administered by the oral route (oral polio vaccine [OPV], oral typhoid) 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. Oral typhoid is not licensed 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, varicella, and yellow fever) and LAIV are not believed to have an effect on live vaccines given by the oral route (OPV, oral typhoid). 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.

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.

Interval Between Doses of the Same Vaccine

Immunizations are recommended for members of the youngest age group at risk for a disease for whom efficacy, immunogenicity, and safety of a vaccine have been demonstrated. Most vaccines in the childhood immunization schedule require two or more doses for stimulation 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 minimal ages and minimal intervals between immunizations for vaccines in the recommended childhood immunization schedule.

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.

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 would be repeated at 12 months of age or older). The second consideration 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 (for example, for an ear recheck). 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 be spaced after the invalid dose by a time greater than the 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 these 4-day recommendations.

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 recom-

Minimum Intervals and Ages

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

Violation of Minimum Intervals or Minimum Age

- ACIP recommends that vaccine doses given up to four 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

mended do not affect seroconversion rate or titer when the schedule was 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. In the case of oral typhoid, some experts recommend repeating the series if the four-dose series is extended to more than 3 weeks.

General Rule

Live attenuated vaccines generally produce long-lasting immunity with a single dose.

Inactivated vaccines require multiple doses and may require periodic boosting to maintain immunity.

Number of Doses

For live injected vaccines, the first dose administered at the recommended age usually provides protection. An additional dose is given to ensure seroconversion. For instance, 95% to 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 production of immunity. Adverse reactions are also called vaccine "side effect". A vaccine **adverse event** refers to *any* adverse event that occurs following vaccination. An adverse event could be a true vaccine 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
  - could be true adverse reaction
  - could 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 50% of vaccine doses, depending on the type of vaccine. Local reactions are most common with inactivated vaccines, particularly those, such as DTaP, that contain adjuvants. 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 because of 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 a vaccinated persons because of the vaccine or may be caused by something unrelated to the vaccine, like a concomitant viral infection.

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 not 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 that replication and are similar to a mild form of the natural disease.

Live Attenuated Vaccines

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

Vaccine Adverse Reactions

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

Systemic adverse reactions following live vaccines are usually mild, and occur a week or two 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, preservatives, or antibiotic used to inhibit bacterial growth. Severe allergic reactions to vaccines may be life-threatening. Fortunately, they are very 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

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 Events 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 events through their online system. (See Chapter 4, Vaccine Safety.)

Contraindications and Precautions to Vaccination

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.

Contraindication

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

A **contraindication** is a condition in a recipient that 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 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 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 vaccination.**

Four conditions are considered permanent precautions to further doses of pediatric pertussis-containing vaccine: temperature greater than 105°F, collapse or shock-like state (hypotonic hyporesponsive episode), 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 following DTaP vaccine is not a precaution to pertussis vaccination of an adolescent or adult.

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** (MMR and varicella only).

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**

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 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
*MMR and varicella 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 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, animal protein, antibiotics, preservatives, or stabilizers. 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, persons who are able to 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 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 Advisory Committee on Immunization Practices 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 anaphylactic reactions to neomycin should not receive these vaccines. Most often, a neomycin allergy reaction is a 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 these vaccines.

Latex is liquid 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 a 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 about vaccinating pregnant women is with 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 given to women known to be pregnant.

Since inactivated vaccines cannot replicate, they cannot cause fetal infection. Inactivated vaccines should be administered to pregnant women for whom they are indicated. Susceptible household contacts of pregnant women should receive MMR and varicella vaccines and may receive LAIV, if eligible.

Immunosuppression

Live vaccines can cause severe or fatal reactions in immunosuppressed persons due to uncontrolled replication of the vaccine virus, particularly vaccinia and oral polio vaccine virus (and rarely measles and varicella vaccine virus). Severely immunosuppressed persons should not be given live vaccines 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.

Immunosuppression

Disease

- **Congenital immunodeficiency**
- **Leukemia or lymphoma**
- **Generalized malignancy**

Immunosuppression

Chemotherapy
- Alkylating agents
- Antimetabolites
- Radiation

Immunosuppression

Corticosteroids
- ≥20 mg per day
- ≥2 mg/kg per day, for ≥ 14 days
- NOT aerosols, alternate-day, short courses, topical

Both diseases and drugs can cause significant immunosuppression. Persons with congenital immunodeficiency, leukemia, lymphoma, or generalized malignancy should not receive live vaccines. OPV should not be given if an immunosuppressed person is in the household. However, MMR, varicella vaccines, and LAIV may be given when an immunosuppressed person lives in the same house.

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.

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 is 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 are not contraindicated for immunosuppressed persons. However, response to the vaccine may be poor. 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 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 are not contraindicated.

Measles and varicella can be very severe illnesses in persons with HIV infection and are often associated with complications. Therefore, measles vaccine (as combination MMR vaccine) and varicella vaccine are recommended 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, MMR, or varicella vaccine. Susceptible household contacts of persons with HIV infection should receive MMR and varicella vaccines. Persons with HIV infection should not receive LAIV; they should receive inactivated influenza vaccine.

Recommendations for Routine Immunization of HIV-Infected Children

Vaccine	Asymptomatic	Symptomatic
Varicella	Yes	No
MMR	Yes	No
LAIV	No	No
All others	Yes	Yes

Yes = vaccinate No = do not vaccinate

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

- Includes recipients of bone marrow, peripheral cell, and umbilical cord blood transplants
- Autologous or allogeneic
- HSCT recipients should be revaccinated

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 for influenza vaccine, which should be administered 6 months after HSCT and annually thereafter for the life of the recipient. MMR vaccine should be administered 24 months after transplantation if the HSCT recipient is presumed to be immunocompetent. Varicella, meningococcal, and pneumococcal conjugate vaccines are not currently recommended for HSCT recipients because of insufficient experience using these vaccines among HSCT recipients.

Vaccination of Hematopoietic Stem Cell Transplant Recipients

- Inactivated influenza vaccine at ≥6 months following transplant and annual thereafter
- Inactivated vaccines (DTaP, Td, Hib, IPV, hepatitis B, PPV) at 12 months
- MMR at 24 months if immunocompetent
- Varicella, meningococcal, and PCV7 vaccines not recommended (insufficient data)

Household and other close contacts of HSCT recipients and healthcare workers 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/nip/publications/hsct-recs.pdf.

Invalid Contraindications to Vaccination

- Minor illness
- Antimicrobial therapy
- Disease exposure or convalescence
- Pregnancy or immunosuppression in the household
- Breastfeeding
- Premature birth
- Non-vaccine-related allergies
- Nonanaphalactic allergy to vaccine component
- Family history (unrelated to immunosuppression)
- Need for TB skin testing

Invalid Contraindications Minor Illness

- Low grade fever
- Upper respiratory infection
- Otitis media
- Mild diarrhea

- ▸ Only one small study has suggested decreased efficacy of measles vaccine in children with URI
- ▸ Findings not replicated by multiple prior and subsequent studies
- ▸ No evidence of increased adverse reaction

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 reaction (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.

Minor, common illnesses (such as otitis media, upper respiratory infections, colds, and diarrhea) are NOT contraindications to vaccination.

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 minor illnesses, conditions related to pregnancy and breastfeeding, allergies that are not anaphylactic in nature, and certain aspects of the patient's family history.

Minor Illness

Children with mild acute illnesses, such as low-grade fever, upper respiratory infection (URI), colds, otitis media, and mild diarrhea, can and **should be vaccinated**.

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. These large studies refute the results of an earlier small study (Krober, *JAMA* 1991) which suggested that minor infections such as URIs might impair the response to measles vaccine. Further, there is no evidence that mild diarrhea reduces the success of immunization of infants in this country.

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.

Antimicrobial Therapy

Antimicrobial agents do not have an effect on the immune response to a vaccine. No commonly used antibiotic or antiviral agent will inactivate a live-virus vaccine.

Disease Exposure or Convalescence

If a child 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.

Pregnancy or Immunosuppression in the Household or Breastfeeding

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, and yellow fever), can be given to infants or children who are household contacts of pregnant or immunosuppressed persons, as well as to breastfeeding infants. Vaccinia (smallpox) vaccine is not recommended for household contacts of a pregnant or immunosuppressed person in nonemergency situations. 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. LAIV may be administered to a woman who is breastfeeding if she is otherwise eligible. The risk of transmission of vaccine virus is not known but is probably low. Breastfeeding does not decrease the response to routine childhood vaccines. Breastfeeding also does not extend or improve the passive immunity to vaccine-preventable disease that is provided by maternal antibody.

Premature Birth

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

Studies demonstrate that decreased seroconversion rates might occur among certain premature infants with low birth weights (less than 2,000 grams) after administration of hepatitis B vaccine at birth. However, by 1 month chronological age, all premature infants, regardless of initial birthweight or gestational age are as likely to respond as adequately as older and larger infants.

All premature 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.

The optimal timing of the first dose of hepatitis B vaccine for premature infants of HBsAg-negative mothers with a birth weight of less than 2,000 grams has not been determined. These infants can begin the first dose of the hepatitis B vaccine series at 1 month of chronological age. Premature infants discharged from the hospital prior to 1 month chronological age may also be given hepatitis B vaccine at discharge if they are medically stable and showing consistent weight gain.

Non–Vaccine-Related Allergies

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.

Nonanaphylactic Allergy to Vaccine Component

Anaphylactic allergy to a vaccine component (such as egg or neomycin) is a true contraindication to vaccination. Nonanaphylactic allergy to a vaccine constituent 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 immunosupression or family history of seizures or sudden infant death syndrome is not a contraindication to vaccination. Varicella virus vaccine 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 immune competence of the potential vaccine recipient has been clinically substantiated or verified by a laboratory.

Tuberculosis Skin Test (PPD)

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

MMR vaccine may decrease the response to a TB skin test, causing a **false-negative** response in someone who actually has an infection with tuberculosis. MMR can be given the same day as a TB skin test, but if MMR has been given and 1 or more days have elapsed, in most situations a wait of 4–6 weeks is recommended before giving a routine TB skin test. No information on the effect of varicella vaccine or LAIV on a TB skin test is available. Until such information is available, it is prudent to apply rules for spacing measles vaccine and TB skin testing to varicella vaccine and LAIV.

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.

Screening Questions

- How is your child today?
- Allergies to food or medication?
- Any problem after last shots?

How is your child (or how are you) today?

This question screens for concurrent moderate or acute illness. If the child has been examined, this question may not be necessary or may have already been asked.

Does your child have any allergies to any food or medication?

A severe allergic reaction to a vaccine component is a contraindication to vaccination, so this question must always be asked. It may be more time-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.

Did the child have any problems after his or her last shots?

This open-ended question explores for allergic reactions to previous doses and for conditions following pertussis vaccine that may be precautions to additional doses, such as high fever or a hypotonic episode.

Does the child have any problems with his or her immune system?

This question will help identify children with immunodeficiency who generally should not receive live attenuated vaccines, particularly oral polio vaccine.

continues

Screening Questions

- Problems with immune system?
- Anyone in household with immune problems?
- Blood products in last year?
- Pregnant?

Does anyone in your household have a problem with their immune system?

Oral polio vaccine should not be given to a healthy person who has household contact with someone who is immunodeficient. LAIV should not be given to household contacts of severely immunosuppressed persons.

Has the child received any blood products in the last year, like a transfusion, or immune globulin?

This question helps identify precautions for live attenuated MMR and varicella vaccines, which should not be given to persons who have received passive antibody in the last few months. The question may also expose unreported illnesses that might not have been revealed in earlier questions.

Are you pregnant, or trying to become pregnant?

This question should be asked of all adolescent and adult women. MMR, varicella, smallpox (vaccinia), and LAIV vaccines should not be given to women known to be pregnant or for 4 weeks prior to pregnancy. Persons with a pregnant household contact should not receive smallpox (vaccinia) vaccine in nonemergency situations. ACIP does not recommend pregnancy testing prior to administration of any vaccine.

Every person should be screened for contraindications and precautions before vaccination. Standardized screening forms for both children and adults, developed by the Immunization Action Coalition, are included in Appendix A.

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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 their lowest level ever. In 2003, only 56 cases of measles, 7 cases of rubella, 1 case of diphtheria, 20 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. 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 workers 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.

Why Focus on Strategies to Increase Immunization?

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

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

Childhood immunization rates are still suboptimal. In 2004, for example, only 85.5% 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 2003, a median of only 70% of persons 65 years of age and older received the influenza vaccine in the past 12 months, and 64.2% 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.

Uptake is lagging for some antigens. In 2004, for example, the percentage of children who had received varicella vaccine by their second birthday was 87.5%. Rates of influenza immunization are also unacceptably low among healthcare workers, an important target population for vaccination. Typically, fewer than 40% of healthcare workers receive influenza vaccine.

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.

Immunization Strategies for Healthcare Practices and Providers

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 National Immunization Program, 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
eXchange

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

Special Characteristics of AFIX

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

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 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

- Evaluation of medical records to ascertain the immunization rate for a defined group
- Diagnosis of potential service delivery problems
- Assessment increases awareness

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

- Informing immunization providers about their performance
- Assessment with feedback creates the awareness necessary for behavior change

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.**

How to Provide Feedback

- With feeling and precision
- Without judgment
- With confidentiality as appropriate

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

eXchange of Information

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

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.

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, NIP 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 is on the NIP website at http://www.cdc.gov/nip/vfc/Default.htm.

AFIX Tools And Training

The National Immunization Program 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 website of the National Immunization Program (http://www.cdc.gov/nip/casa/). 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 website of the National Immunization Program (http://www.cdc.gov/nip/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 recently revised 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 still in its infancy and 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 Registries

Many recordkeeping tasks, as well as patient reminder/recall activities, can be greatly simplified by participation in a population-based immunization registry, also known as an immunization information system. An immunization registry 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 immunization registry is linked to a child's complete medical record. A registry 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.

Immunization Registries

- Single data source for all providers
- Reliable immunization history
- Produce records for patient use
- Key to increasing immunization levels

Registries 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 providers' 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 2002, approximately 43% of children in this age-group met this participation goal, and NIP and its partners at the federal, state and local levels 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 NIP's website at http://www.cdc.gov/nip/registry/gen.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.

Recommendations and Reinforcement

- Recommend the vaccine
  - —powerful motivator
  - —patients likely to follow recommendation of the provider
- Reinforce the need to return
  - —verbal
  - —written
  - —link to calendar event

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.

Reminders 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 Immunization Program 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.

Reminders 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 over age 65.

- 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 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).

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:

- **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.

Missed Opportunity

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

Reasons for Missed Opportunities

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

Strategies for Reducing Missed Opportunities

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

- **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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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. Thus, 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,

Importance of Vaccine Safety

- Decreases in disease risks and increased attention on vaccine risks
- Public confidence in vaccine safety is critical
  - higher standard of safety is expected of vaccines
  - vaccinees generally healthy (vs. ill for drugs)
  - lower risk tolerance = need to search for rare reactions
  - vaccination universally recommended and mandated

Importance of Vaccine Safety

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

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 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.

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. Most recently, a clinical immunization safety assessment network has been 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 workers 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). A recent classification divides vaccine adverse events as follows:

- **Vaccine-induced:** Due to the intrinsic characteristic of the vaccine preparation and the individual response of the

Adverse Event Classification

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

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.

Large-Linked Databases

Historically, when a signal of a potential vaccine safety concern was generated from passive surveillance, further ad hoc studies were needed to test the hypothesis. Such studies, while potentially informative about vaccine causality, were costly, time-consuming, and usually limited to assessment of a single event. The need to improve postlicensure monitoring of drug safety became widely recognized in the 1960s following the discovery that thalidomide, a licensed drug commonly used during pregnancy, caused severe birth defects. The inability of passive surveillance systems to determine clear causal relationships, and the lack of timeliness of ad hoc studies to evaluate vaccine adverse events highlighted the need for an active surveillance system using large-linked databases (LLDBs). Pharmacoepidemiologists during the 1980s began to establish and utilize large databases

linking computerized pharmacy prescription (and later, immunization records) and computerized medical records. These LLDBs are derived from defined populations such as members of health maintenance organizations (HMOs), single-provider healthcare systems, and Medicaid programs. Because these databases are usually generated in the routine administration of such programs and do not require completion of a vaccine adverse event reporting form, the problems of underreporting or recall bias, which are sometimes seen with passive surveillance systems like VAERS, are reduced. Therefore, LLDBs can potentially provide an economical and rapid means of conducting postlicensure studies of safety of drugs and vaccines. **CDC's Vaccine Safety Datalink (VSD)** project is one example of such a system. It links the immunization and medical records of members of eight HMOs, comprising more than 5.5 million persons (approximately 2% of the U.S. population) annually, for various vaccine safety studies. Further information about LLDBs is available at http://www.cdc.gov/nip/vacsafe.

Vaccine Safety Datalink (VSD)

- Large-linked database
- Links vaccination and health records
- "Active surveillance"
  - 8 HMOs
  - ~2% 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 Program (VICP)

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

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.

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.

The VICP has received more than 7,000 claims since its effective date of October 1, 1988. 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/osp/vicp/

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

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 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.

The Provider's Role

- **Immunization providers can help to ensure the safety and efficacy of vaccines through proper:**
  - **–management of vaccine side effects**
  - **–reporting of suspected side effects to VAERS**
  - **–vaccine benefit and risk communication**

- 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
- Pregnancy or immunosuppression 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
- Convalescent phase of illness
- Recent exposure to infectious disease

- 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 www.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

- Opportunities for questions should be provided before each vaccination
- Vaccine Information Statements (VISs)
  - must be provided before each dose of vaccine
  - public and private providers
  - available in multiple languages

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 (VIS)**," 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 National Immunization Program website at http://www.cdc.gov/nip 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 professionals 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 National Immunization Program's website contains extensive and up-to-date information on vaccine safety issues (http://www.cdc.gov/nip/menus/vacc_safety.htm).

When a parent or patient initiates discussion regarding a vaccine concern, the healthcare professional 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. Fact sheets, titled, "Vaccines a Safe Choice" and "Helping Parents Who Question Vaccines" (available at http://www.cdc.gov/nip) may also be helpful.

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 unimmunized 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.

Acknowlegements

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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

Diphtheria

Pharyngeal and Tonsillar Diphtheria

- Insidious onset of exudative pharyngitis
- Exudate spreads within 2-3 days and may form adherent membrane
- Membrane may cause respiratory obstruction
- Fever usually not high but patient appears toxic

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:

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.

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% for respiratory disease

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 National Immunization Program during office hours (8:00 a.m.–4:30 p.m. ET) at 404-639-8257, or at all other times through CDC's Director'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 non-toxigenic, 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

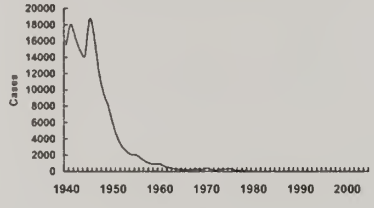
Human carriers are the reservoir for *C. diphtheriae* and are usually asymptomatic. In outbreaks, high percentages of children are found to be transient carriers.

Transmission

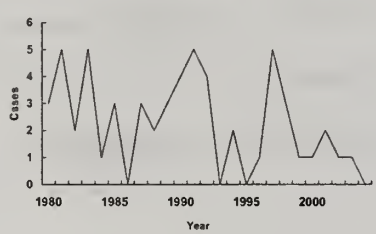
Transmission is most often person-to-person spread from the respiratory tract. Rarely, transmission may occur from skin lesions or articles soiled with discharges from lesions of infected persons (fomites).

Diphtheria

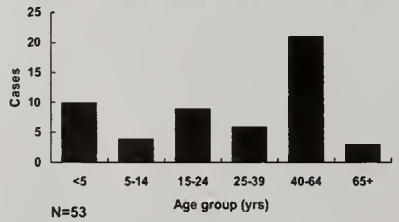
Diphtheria - United States, 1940-2004



Diphtheria - United States, 1980-2004



Diphtheria – United States, 1980-2004
Age Distribution of Reported Cases



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 socioeconomic strata.

From 1980 through 2004, 57 cases of diphtheria were reported in the United States, an average of 2–3 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 DT or adult Td, and with both tetanus toxoid and acellular pertussis vaccine as DTaP and Tdap. Diphtheria toxoid is also available as a combined DTaP-inactivated poliovirus (IPV)-hepatitis B combination (Pediarix—see the pertussis chapter for more information). Pediatric formulations (DT and DTaP) contain a similar amount of tetanus toxoid as adult Td, but contain 3–4 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 children 10–18 years of age) and Adacel (approved for persons 11–64 years of age). DTaP and Tdap vaccines do not contain thimerosal as a preservative.

DTaP, DT, and Td

	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 11-64 years (Adacel)

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

Diphtheria

Routine DTaP Primary Vaccination Schedule

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

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 <12 months of age, 4 doses are recommended
  - —if first dose given at ≥12 months, 3 doses complete the primary series

Routine DTaP Schedule Children <7 years of age

Booster Doses

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

Routine Td Schedule Unvaccinated Persons ≥7 Years of Age

Dose*	Interval
Primary 1	---
Primary 2	4 wks
Primary 3	6-12 mos

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 4–6 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 11–12 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 6–12 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.

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

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 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.

Diphtheria and Tetanus Toxoids Adverse Reactions

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

Contraindications and Precautions to Vaccination

Persons with a history of a **severe allergic reaction** following a prior dose should not receive additional doses of diphtheria toxoid. Diphtheria toxoid should be deferred for those

Diphtheria and Tetanus Toxoids Contraindications and Precautions

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

persons who have **moderate to 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.

Vaccine Storage and Handling

DTaP, DT (pediatric), Td, DTP/Hib, Tdap, and tetanus toxoid should be stored continuously at 35°–46°F (2°–8°C). The vaccine may be out of refrigeration for as long as 4 days, but it should be refrigerated immediately when received. 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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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

Tetanus Pathogenesis

- Anaerobic conditions allow germination of spores and production of toxins
- Toxin binds in central nervous system
- Interferes with neurotransmitter release to block inhibitor impulses
- Leads to unopposed muscle contraction and spasm

6

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.

Tetanus Clinical Features

- Incubation period; 8 days (range, 3-21 days)
- Three clinical forms: local (not common), cephalic (rare), generalized (most common)
- Generalized tetanus: descending symptoms of trismus (lockjaw), difficulty swallowing, muscle rigidity, spasms
- Spasms continue for 3-4 weeks; complete recovery may take months

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

- Generalized tetanus in newborn infant
- Infant born without protective passive immunity
- Estimated >215,000 deaths worldwide in 1998

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 215,000 deaths worldwide in 1998), 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 <3 doses	Yes	No	Yes	Yes
3+ doses	No*	No	No**	No

* Yes, if >10 years since last dose
** Yes, if >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 table, Tetanus Wound Management). 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 toxoid. 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

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

Occurrence

Tetanus occurs worldwide but is most frequently encountered in densely populated regions in hot, damp climates with soil rich in organic matter.

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. 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) were reported in 2003.

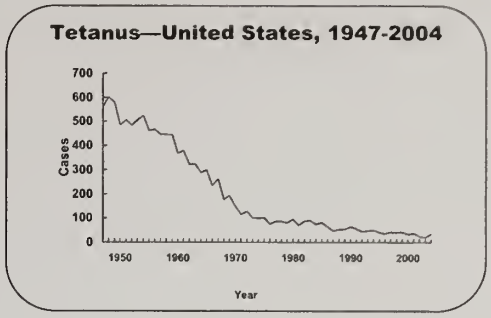
From 1980 through 2000, 70% of reported cases of tetanus were among persons 40 years of age or older. From 1980 through 1990, a median of 21% of reported cases were among persons younger than 40 years of age. The age distribution of reported cases shifted to a younger age group in the last half of the 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.

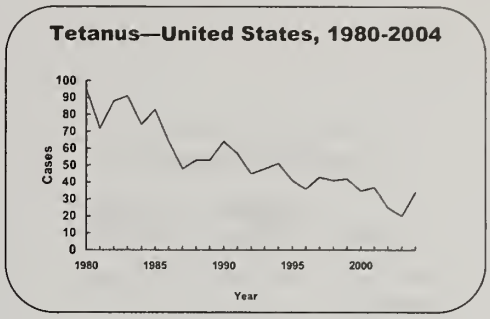
Almost all reported cases of tetanus are in persons who have either never been vaccinated, or who completed a primary series but have not had a booster in the preceding 10 years.

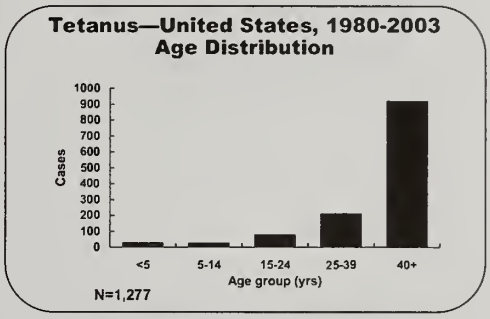
Heroin users, particularly persons who inject themselves subcutaneously, appear to be at high risk for tetanus. Quinine is used to dilute heroin and may support the growth of C. *tetani*.

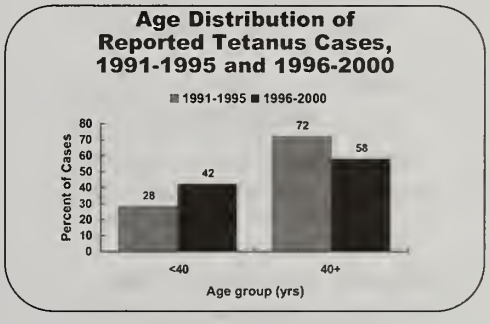
Neonatal tetanus is rare in the United States, with only two cases reported since 1989. Neither of the infants' mothers had ever received tetanus toxoid.

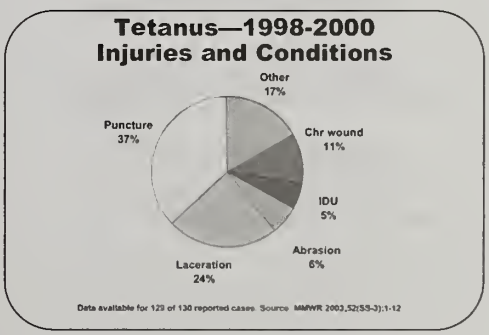
During 1998–2000 (the most recent years for which data are available), acute injuries or wounds preceded tetanus in 94 (73%) of the 129 cases for which information was available. Among the most frequent wound types were puncture wounds (50%), lacerations (33%), and abrasions (9%). The most common puncture 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.

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 is available as a single-antigen preparation, combined with diphtheria toxoid as pediatric DT or adult Td, and with both diphtheria toxoid and acellular pertussis vaccine as DTaP or Tdap. Tetanus toxoid is also available as a combined DTaP-IPV-hepatitis B combination (Pediarix—see Chapter 7, Pertussis, for more information). Pediatric formulations (DT and DTaP) contain a similar amount of tetanus toxoid as adult Td, but contain 3–4 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 children 10–18 years of age) and Adacel (approved for persons 11–64 years of age). DTaP and Tdap vaccines do not contain thimerosal as a preservative.

DTaP, DT, and Td

	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 11-64 years (Adacel)

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

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 minimal protective level of 0.01 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 to 7 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.

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.

Routine DTaP Primary Vaccination Schedule

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

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 <12 months of age, 4 doses are recommended
  - —if first dose given at ≥12 months, 3 doses complete the primary series

Routine DTaP Schedule
Children <7 years of age

Booster Doses

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

Routine Td Schedule
Unvaccinated Persons ≥7 Years of Age

Dose*	Interval
Primary 1	---
Primary 2	4 wks
Primary 3	6-12 mos

Booster dose every 10 years

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

Diphtheria and Tetanus Toxoids
Adverse Reactions

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

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 11–12 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.

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.

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. Following a recent review, the Institute of Medicine concluded that the available evidence favors a causal relationship between tetanus toxoid and both brachial neuritis and GBS, although these reactions are very rare.

See Chapter 7, Pertussis, for additional information on contraindications and precautions to Tdap.

Contraindications and Precautions to Vaccination

A severe allergic reaction (acute respiratory distress or collapse) 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.

Diphtheria and Tetanus Toxoids Contraindications and Precautions

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

Vaccine Storage and Handling

DTaP, DT (pediatric), Td, DTP/Hib, Tdap, and tetanus toxoid should be stored continuously at 35°–46°F (2°–8°C). The vaccine may be out of refrigeration for as long as 4 days, but it should be refrigerated immediately when received. Freezing reduces the potency of the tetanus component. Vaccine exposed to freezing temperature should never be administered.

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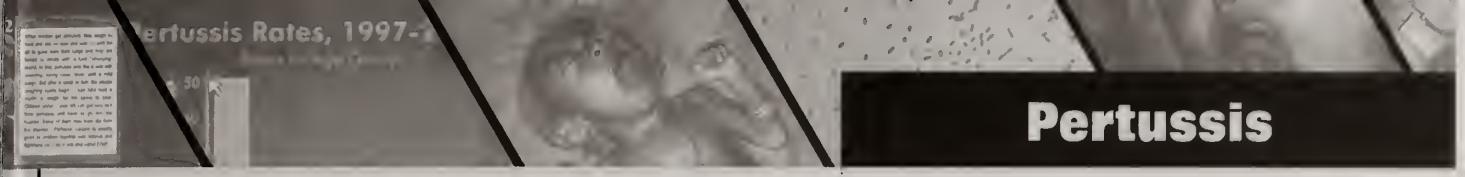

Pertussis

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 an estimated 285,000 deaths resulting from the disease in 2001.

Pertussis

- Highly contagious respiratory infection caused by *Bordetella pertussis*
- Outbreaks first described in 16th century
- *Bordetella pertussis* isolated in 1906
- Estimated 285,000 deaths worldwide in 2001

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 to subsequent clinical illness. Recent evidence suggests that immunity from *B. pertussis* infection is not permanent.

Bordetella pertussis

- Fastidious gram-negative bacteria
- Antigenic and biologically active components:
  - pertussis toxin (PT)
  - filamentous hemagglutinin (FHA)
  - agglutinogens
  - adenylate cyclase
  - pertactin
  - tracheal cytotoxin

Pathogenesis

Pertussis is primarily a toxin-mediated disease. The bacteria attach to the respiratory cilia, 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.

Pertussis Pathogenesis

- Attachment to cilia of ciliated epithelial cells in respiratory tract
- Pertussis antigens allow evasion of host defenses (lymphocytosis promoted but impaired chemotaxis)
- Local tissue damage in respiratory tract
- Systemic disease may be toxin mediated

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

- Incubation period 7-10 days (range 4-21 days)
- Insidious onset, similar to minor upper respiratory infection with nonspecific cough
- Fever usually minimal throughout course of illness

Pertussis

Pertussis Clinical Features

• Catarrhal stage	1-2 weeks
• Paroxysmal cough stage	1-6 weeks
• Convalescence	Weeks to months

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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.

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 patient usually appears normal 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. Fever is generally minimal throughout the course of the illness.

Pertussis Among Adolescents and Adults

- Disease often milder than in infants and children
- Infection may be asymptomatic, or may present as classic pertussis
- Adolescents and adults account for more than half of reported cases
- Older persons often source of infection for children

Older persons (i.e., **adolescents and adults**) and those partially protected by the vaccine may become infected with *B. pertussis* but often have milder disease. 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 uncommon. Adolescents and adults have accounted for more than half of reported pertussis cases in recent years.

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 underimmunized infants. Older persons are often found to have the first case in a household with multiple pertussis cases.

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

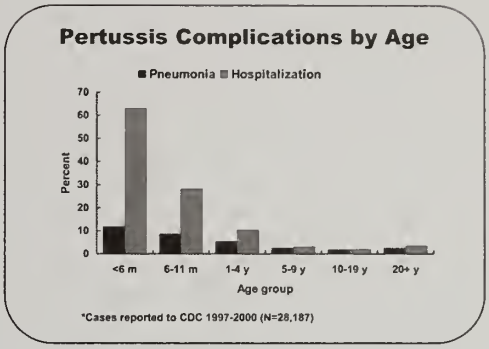
Young infants are at highest risk for acquiring pertussis-associated complications. The most common complication, and the cause of most pertussis-related deaths, is secondary

bacterial pneumonia. 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.

Among persons of all ages with pertussis, 33 cases of encephalopathy and 56 pertussis-related deaths were reported during 2001–2003. Fifty-one (91%) of the deaths were among infants younger than 6 months of age, and 42 (75%) were among infants aged younger than 2 months of age.

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 usually based on a characteristic history and physical examination. However, laboratory tests may be useful with young infants, atypical cases, and cases modified by vaccine.

The standard and preferred laboratory test for diagnosis of pertussis is **isolation of *B. pertussis* by culture**. A positive culture for *B. pertussis* confirms the diagnosis. However, fastidious growth requirements make *B. pertussis* difficult to isolate. Isolation of the organism using direct plating is most successful during the catarrhal stage. Specimens from the posterior nasopharynx, not the throat, should be obtained using Dacron® or calcium alginate (not cotton) swabs and should be plated directly onto selective media. Success in isolating the organism declines if the patient has had prior antibiotic therapy effective against pertussis (erythromycin or trimethoprim-sulfamethoxazole), if specimen collection is delayed beyond the first 2 weeks of illness, or if the patient has been vaccinated.

Polymerase chain reaction (PCR) testing of nasopharyngeal swabs or aspirates can be a rapid, sensitive, and specific method for diagnosing pertussis. Currently, it is available only in certain laboratories; the assays vary among laboratories and are not standardized. PCR should be used in addition to culture, not as a replacement for culture, because bacterial isolates may be required for evaluation of antimicrobial resistance or for molecular typing.

Direct fluorescent antibody (DFA) testing of nasopharyngeal specimens may be useful as a screening test for pertussis. Because DFA testing of nasopharyngeal secretions has been shown in some studies to have low sensitivity and variable specificity, it should not be relied on as a criterion for laboratory confirmation.

Serologic testing has proved useful in clinical studies but is not yet standardized. Because of the lack of association between antibody levels and immunity to pertussis, results of serologic testing are difficult to interpret. For these reasons, serologic testing is not widely available. In some areas, it is used for clinical diagnosis and reporting, but in the absence of standardization, serologic test results should not be relied upon for case confirmation for the purpose of national reporting.

An elevated white blood cell count with a lymphocytosis is usually present in classical disease. The absolute lymphocyte count often reaches 20,000 or greater. However, there may be no lymphocytosis in infants and children or in persons with mild or modified cases of pertussis.

More information on the laboratory diagnosis of pertussis is available on the National Immunization Program website.

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 selected 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. (minimum age for first dose is 6 weeks; minimum intervals from dose 1 to 2 and from dose 2 to 3 are 4 weeks; minimum interval from dose 3 to 4 is 6 months.) 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.

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. A silent carrier state is thought to exist, but it is infrequent, transient in duration, and probably of little importance in maintaining pertussis organisms in the community.

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).

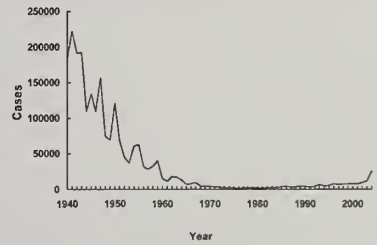
Secular Trends in the United States
Before the availability of vaccine, pertussis was a common cause of morbidity and mortality among children. During the 6-year period from 1940 through 1945, more than 1 million cases of pertussis were reported, an average of 175,000 cases per year (incidence of approximately 150 cases per 100,000 population).

Following introduction of vaccine in the 1940s, pertussis incidence gradually declined, reaching 15,000 reported cases in 1960 (~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 (~1 per 100,000 population).

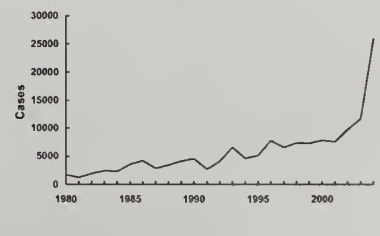
Pertussis Epidemiology

• Reservoir	Human Adolescents and adults
• Transmission	Respiratory droplets
• Communicability	Maximum in catarrhal stage Secondary attack rate up to 80%

Pertussis—United States, 1940-2004

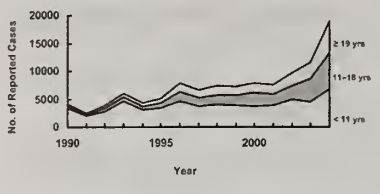


Pertussis—United States, 1980-2004



Pertussis

Reported Pertussis by Age Group, 1980-2004*



*2004 data provisional
National Immunization Program unpublished data

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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 but may be a reflection of the 3–5 year cyclicity observed with the disease.

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 (20 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, approximately 60% of 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 on the National Immunization Program website at http://www.cdc.gov/nip/publications/pertussis/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/nip/publications/surv-manual/) for more information on case classification.

Both probable and confirmed cases should be reported to the National Notifiable Diseases Surveillance System (NNDSS).

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.

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

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% to 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. More severe systemic reactions, such as convulsions and hypotonic hyporesponsive episodes occurred less frequently (one case per 1,750 doses administered). Acute encephalopathy occurred even more rarely (0–10.5 cases per million doses administered). Experts disagreed on whether whole-cell pertussis vaccine caused lasting brain damage, but they agreed that if the vaccine caused such damage, it did so only rarely. Concerns about safety led to the development of more purified (acellular) pertussis vaccines that are associated with a lower frequency of adverse reactions.

Acellular Pertussis Vaccines

- Purified "subunit" vaccines
- Pediatric formulations (DTaP) licensed for full series in 1996
- Adolescent and adult formulations (Tdap) licensed in 2005

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

DTaP Clinical Trials

Product	Location	VE (95% CI)
Daptacel	Sweden	85% (80-89)
Tripedia	Germany	80% (59-90)
Infanrix	Italy	84% (76-89)

Acellular Pertussis Vaccine

Characteristics

Acellular pertussis vaccines 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]

Pediatric formulations of acellular pertussis vaccines were first licensed for the fourth and fifth doses of the pertussis series in 1991, and for the primary series in 1996. 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. 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, pertacin, 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.

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) was licensed in May 2005 and contains three pertussis antigens (PT, FHA, and pertactin) in a reduced quantity from the GlaxoSmithKline pediatric formulation. The vaccine contains aluminum hydroxide as an adjuvant and does not contain a preservative. Adacel (sanofi pasteur) was licensed in June 2005. It contains same five 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 as single-dose vials or syringes.

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 be made with caution. Point estimates of vaccine efficacy ranged from 80% to 85% for vaccines 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

Acellular pertussis vaccine (DTaP) is recommended for all doses of the pertussis schedule. Whole-cell vaccine (DTP) is no longer available in the United States. The primary series of DTaP consists of four doses of vaccine, 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.

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.

Routine DTaP Primary Vaccination Schedule

Dose	Age	Minimum Interval
Primary 1	2 months	---
Primary 2	4 months	4 wks
Primary 3	6 months	4 wks
Primary 4	15-18 months	6 mos

DTaP Fourth Dose

- Recommended at 15-18 months*
- May be given at 12 months of age 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

School Entry (Fifth) Dose

- Fifth dose recommended when 4th dose given before age 4 years
- Infanrix and Tripedia licensed for 5th dose after DTaP series

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 if the fourth dose in the primary series was given on or after the fourth birthday. The booster dose increases protective antibody levels and may decrease the risk of school-age children transmitting the disease to younger siblings who are not fully vaccinated. Tripedia and Infanrix are approved for the fifth dose following a series of four doses of DTaP.

For children who have 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

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. The two vaccines are approved for use in different age groups: Boostrix is approved for persons 10–18 years of age; Adacel is approved for persons 11–64 years of age.

Provisional ACIP Recommendations for Tdap Vaccines

- Adolescents 11-18 years of age should receive a single dose of Tdap instead of Td, preferably at 11-12 years of age*
- Adolescents who received a Td booster should receive a single dose of Tdap to provide protection against pertussis*

*if the person has completed the recommended childhood DTaP/DTP vaccination series

At the time of publication of this book (January 2006) ACIP recommendations for the use of Tdap vaccines for adolescents and adults have not been published. Provisional recommendations are that adolescents 11–18 years of age should receive a single dose of Tdap instead of Td, preferably at 11–12 years of age. Adolescents aged 11–18 years who received Td but not Tdap are encouraged to receive a single dose of Tdap to provide protection against pertussis. A 5-year interval between Td and Tdap is encouraged to reduce the risk of local and systemic adverse reactions. However, Tdap may be given at an interval of less than 5 years if the benefits

of protection from pertussis outweigh the risk of an 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 desired because of close contact with an infant younger than 6 months of age or a young child who has not been vaccinated against pertussis.

Provisional recommendations for vaccination of adults are for a single dose of Tdap to replace a single dose of Td for booster immunization against tetanus, diphtheria, and pertussis if the most recent tetanus toxoid-containing vaccine was received at least 10 years earlier. Tdap may be given at an interval shorter than 10 years since receipt of the last tetanus toxoid-containing vaccine if necessary to protect against pertussis. Adults who have or who anticipate having close contact with an infant 12 months of age or younger (e.g., parents, child care providers, healthcare providers) should receive a single dose of Tdap. An interval of 2 years or more since the most recent tetanus toxoid-containing vaccine is suggested for these adults; shorter intervals may be used. Ideally, Tdap should be given at least 1 month before beginning close contact with the infant. Women should receive a dose of Tdap in the immediate postpartum period if they have not previously received Tdap. Any woman who might become pregnant is encouraged to receive a single dose of Tdap.

Provisional ACIP Recommendations for Tdap Vaccines

- Adults should receive a single dose of Tdap to replace a single dose of Td*
- Adults who have or who anticipate having close contact with an infant 12 months of age or younger (e.g., parents, child care providers, healthcare providers) should receive a single dose of Tdap*
- Any woman who might become pregnant is encouraged to receive a single dose of Tdap

*If the person has completed the recommended childhood DTaP/DTP vaccination series

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 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

One combination DTaP–Hib (*Haemophilus influenzae* type b) vaccine is available in the United States (TriHIBit,

TriHIBit

- DTaP-Hib combination
- Do not use for primary immunization at 2, 4, or 6 months of age
- May be used as the booster dose of the Hib series at ≥12 months of age following any Hib vaccine*

*booster dose should follow prior dose by ≥2 months

sanofi pasteur). 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.

Because of evidence of reduced immunogenicity of the Hib component when used as a combination, 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). Therefore, TriHIBit can be used if the child is 12 months of age or younger, 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 15–59 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

- DTaP – Hep B – IPV combination
- Approved for 3 doses at 2, 4 and 6 months
- Not approved for booster doses
- Licensed for children 6 weeks to 7 years of age

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 itself 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 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 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

- May be used interchangeably with other pertussis-containing vaccines if necessary
- Can be given at 2, 4, and 6 months in 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 unknown

Other DTaP Issues

Infants and children with **underlying neurologic conditions** present a unique problem, whether these conditions are fully recognized or only possible or potential. These children appear to be at increased risk for manifesting the underlying neurologic disorder within 2–3 days after vaccination. However, more prolonged manifestations or increased progression of the disorder or exacerbation of the disorder have not been recognized.

In certain circumstances, vaccination with DTaP vaccine should be delayed until the child 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 these children at the time of DTaP vaccination and for 24 hours thereafter to reduce the possibility of postvaccination fever.

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 pertussis vaccine
- Satisfactory documentation of disease:
  - —recovery of *B. pertussis* on culture, or
  - —typical symptoms and clinical course when epidemiologically linked to a culture-proven case

DTaP Adverse Reactions

- Local reactions (pain, redness, or swelling at the site of injection)
- Low-grade fever
- More severe adverse reactions not common
- Local reactions more common following 4th and 5th doses

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 pertussis vaccine. 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 other *Bordetella* species, other bacteria, or certain viruses.

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 occur after either whole-cell DTP vaccination or DTaP vaccination. However, mild reactions following the first four doses are less common among children who receive DTaP. For instance, fever of higher than 101oF is reported in 3%–5% of DTaP recipients compared with 16% of recipients of whole-cell DTP. These reactions are self-limited and can be managed with symptomatic treatment with acetaminophen or ibuprofen. **Moderate or severe systemic events** (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 among children administered DTaP than among children administered 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., 2003) 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.

In the absence of a vaccine supply shortage, ACIP continues to recommend 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.

Despite the increased reactogenicity of the fourth and fifth doses, DTaP remains the preferred vaccine for preventing pertussis, diphtheria, and tetanus among children because of the improved safety profile when compared with whole-cell pertussis vaccines.

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 redness or swelling at the site of injection. Vaccine recipients also reported low-grade fever and 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, or swelling at the site of injection)
- Low-grade fever
- Adverse reactions occur at approximately the same rate as Td alone (without acellular pertussis vaccine)

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, 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

Tdap Precautions

- History of Guillain-Barré syndrome within 6 weeks after a previous dose of tetanus toxoid-containing vaccine
- Progressive neurological disorder until the condition has stabilized
- History of a severe local reaction (Arthus reaction) following a prior dose of a tetanus and/or diphtheria toxoid-containing vaccine
- Moderate or severe acute illness

Contraindications and Precautions to Vaccination

DTaP

Contraindications to further vaccination with DTaP are **severe allergic reaction** 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 pertussis vaccination are considered to be precautions for subsequent doses of pertussis vaccine. These adverse reactions are **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 may be 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 may 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 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 contraindication 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.

Vaccine Storage and Handling

DTaP 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 and Tdap should not be used after the expiration date printed on the box or label.

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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
- >21,000 paralytic cases reported in the U.S. in 1952
- Global eradication in near future

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

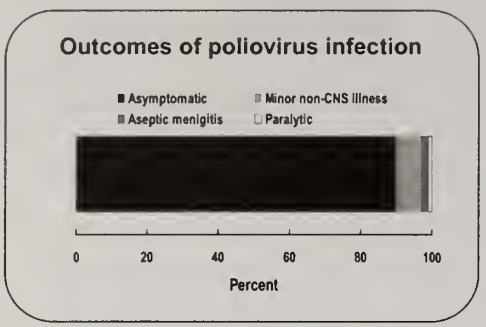
Pathogenesis

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

Poliomyelitis



Clinical Features

The **incubation period** for poliomyelitis is commonly 6–20 days with a range of 3–35 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/mm^3, 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 2003, only 784 confirmed cases of polio were reported globally and polio was endemic in six countries.

Poliovirus Epidemiology

• Reservoir	Human
• Transmission	Fecal-oral Oral-oral possible
• Communicability	7-10 days before onset Virus present in stool 3-6 weeks

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.

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.

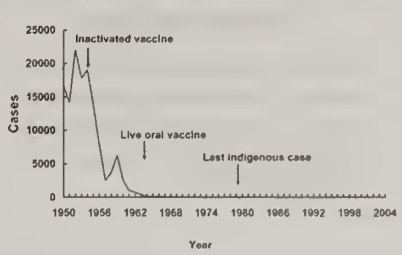
In the early vaccine era, the incidence dramatically decreased after the introduction of inactivated polio vaccine (IPV) 1955. The decline continued following oral polio vaccine (OPV) introduction in 1961. In 1960, a total of 2,525 paralytic cases were reported, compared with 61 in 1965.

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.

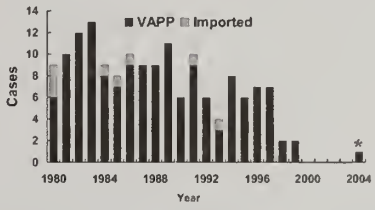
From 1980 through 1999, a total of 152 confirmed cases of paralytic poliomyelitis were reported, an average of 8 cases per year. Six cases were acquired outside the United States and imported. The last imported case was reported in 1993. Two cases were classified as indeterminant (no poliovirus isolated 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.

Poliomyelitis—United States, 1950-2004



Poliomyelitis—United States, 1980-2004



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.

Poliovirus Vaccine

- 1955 Inactivated vaccine
- 1961 Types 1 and 2 monovalent OPV
- 1962 Type 3 monovalent OPV
- 1963 Trivalent OPV
- 1987 Enhanced-potency IPV (IPV)

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.

Inactivated Polio Vaccine

- Contains 3 serotypes of vaccine virus
- Grown on monkey kidney (Vero) cells
- Inactivated with formaldehyde
- Contains 2-phenoxyethanol, neomycin, streptomycin, polymyxin B

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

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.

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 Polio Vaccine

- Highly effective in producing immunity to poliovirus
- ≥90% immune after 2 doses
- ≥99% immune after 3 doses
- Duration of immunity not known with certainty

Inactivated poliovirus vaccine

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 Polio Vaccine

- Highly effective in producing immunity to poliovirus
- ~50% immune after 1 dose
- >95% immune after 3 doses
- Immunity probably lifelong

Oral poliovirus vaccine

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.

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.

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.

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.

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

Polio Vaccination Recommendations

- Exclusive use of IPV recommended in 2000
- OPV no longer routinely available in the United States
- Indigenous VAPP eliminated

Polio Vaccination Schedule

Age	Vaccine	Minimum Interval
2 months	IPV	---
4 months	IPV	4 wks
6-18 months	IPV	4 wks
4-6 years*	IPV	4 wks

*the fourth dose of IPV may be given as early as 18 weeks 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 months. 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.

Pediarix

- Contains IPV, DTaP, and hepatitis B vaccines
- Minimum age 6 weeks, maximum age 6 years
- Approved by FDA for first 3 doses of the IPV and DTaP series
- Not approved for booster doses

In 2002, a pentavalent (5-component) combination vaccine (**Pediarix**) containing IPV was approved for use in the United States. The vaccine also contains DTaP and a pediatric dose of hepatitis B vaccine. The minimum age for the first dose of Pediarix is 6 weeks (as it is for IPV and DTaP). **Pediarix is approved only for the first three doses of the DTaP and IPV series**, which are usually given at about 2, 4, and 6 months of age. However, Pediarix is approved for use through 6 years of age, the same as the DTaP component. 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. Pediarix is not approved for fourth dose of the IPV series, or the fourth or fifth (booster) doses of the DTaP series.

Polio Vaccination of Adults

- Routine vaccination of U.S. residents ≥18 years of age not necessary or recommended
- May consider vaccination of travelers to polio-endemic countries and selected laboratory workers

Polio Vaccination of Adults

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 workers 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 1–2 months, and a third dose given 6–12 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 4–8 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.

- **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 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

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

Polio Vaccine Adverse Reactions

- Rare local reactions (IPV)
- No serious reactions to IPV have been documented
- Paralytic poliomyelitis (OPV)

Vaccine-Associated Paralytic Polio

- Increased risk in persons ≥18 years
- 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

Vaccine-Associated Paralytic Polio (VAPP) 1980-1998

• Healthy recipients of OPV	41%
• Healthy contacts of OPV recipients	31%
• Community acquired	5%
• Immunodeficient	24%

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.

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.

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 immunologically normal. 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.

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 immunologically normal 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 above a U.S. resident with VAPP was reported in 2005, but the vaccine virus infection was acquired in Costa Rica.

Contraindications And Precautions To Vaccination

Severe allergic reaction 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.

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).

Polio Vaccine Contraindications and Precautions

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

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 the National Immunization Program, 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. The last isolation of type 2 virus was in India in October 1999.

Polio Eradication

- Last case in United States in 1979
- Western Hemisphere certified polio free in 1994
- Last isolate of type 2 poliovirus in India in October 1999
- Global eradication goal

Wild Poliovirus 1988

Wild Poliovirus 2004

The polio eradication initiative is supported by a coalition of international organizations that includes WHO, the United Nations Children's Fund (UNICEF), and other bilateral and multilateral organizations. Rotary International has contributed more than $500 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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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

Haemophilus Influenza Type b

***Haemophilus influenzae* type b Pathogenesis**

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

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 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 pre-vaccine 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.

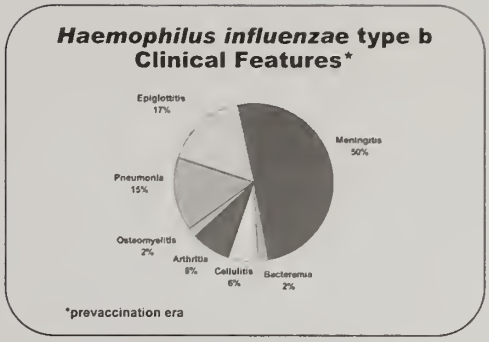
Septic arthritis (joint infection), **cellulitis** (rapidly progressing skin infection which usually involves face, head, or neck), and **pneumonia** (which can be mild focal or severe empyema) are common manifestations of invasive disease.

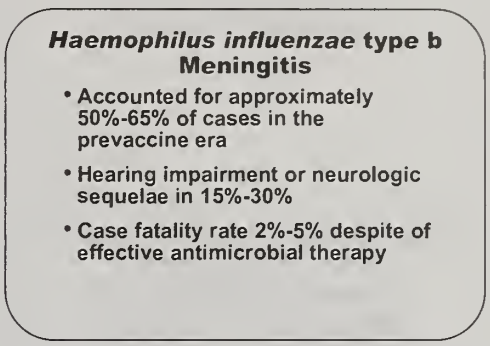
Osteomyelitis (bone infection) and **pericarditis** (infection of the sac covering the heart) are less common forms of invasive disease. Otitis media and acute bronchitis due to *H. influenzae* are generally caused by nontypeable strains. Hib strains account for only 5%–10% of *H. influenzae* causing 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 than15 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.

***Haemophilus influenzae* type b**
Medical Management

- Hospitalization required
- Treatment with an effective 3rd generation cephalosporin, or chloramphenicol plus ampicillin
- Ampicillin-resistant strains now common throughout the United States

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.

***Haemophilus influenzae* type b**
Epidemiology

• Reservoir	Human Asymptomatic carriers
• Transmission	Respiratory droplets
• Temporal pattern	Peaks in Sept-Dec and March-May
• Communicability	Generally limited but higher in some circumstances

Epidemiology

Occurrence

Hib disease occurs worldwide. However, the incidence outside the United States and Europe has not been determined.

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.

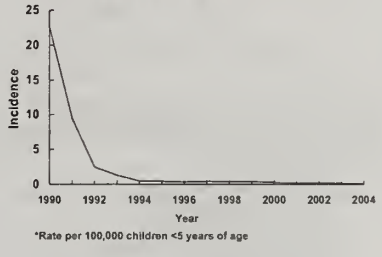
From 1996 through 2000, an average of 1,247 invasive *H. influenzae* infections per year were reported to CDC in all age groups (range 1,162–1,398 per year). Of these, an average of 272 (approximately 22%) per year were among children younger than 5 years of age. Serotype was known for 76% of the invasive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

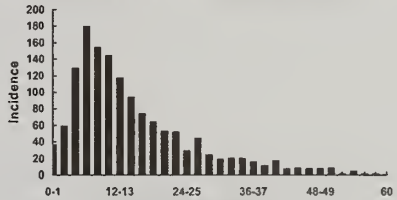
In 1998–2000, approximately 44% of children younger than 5 years of age with confirmed invasive Hib disease were younger than 6 months of age and too young to have

Incidence*of Invasive Hib Disease, 1990-2004



*Rate per 100,000 children <5 years of age

***Haemophilus influenzae* type b, 1986 Incidence* by Age Group**



*Rate per 100,000 population, prevaccine era

***Haemophilus influenzae* type b— United States, 1996-2000**

- Incidence has fallen 99% since prevaccine era
- 341 confirmed Hib cases reported during 1996-2000 (average of 68 cases per year)
- Most recent cases in unvaccinated or incompletely vaccinated children

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.

In 2004, among children younger than 5 years of age, 19 cases of invasive disease due to Hib were reported in the United States. In addition, another 177 cases caused by unknown *H. influenzae* serotypes were reported, so the actual number of Hib cases could be between 19 and 196. 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 diseases (e.g., sickle cell anemia, antibody deficiency syndromes, malignancies, especially during chemotherapy), and possibly gender (risk is higher for males).

***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

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 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.

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.

The first Hib conjugate vaccine (PRP-D, ProHIBIT) was licensed in December 1987. This vaccine was not consistently immunogenic in children younger than 18 months of age. PRP-D is no longer available in the United States.

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

Haemophilus influenzae type b Polysaccharide Vaccine

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

Polysaccharide Vaccines

- Age-related immune response
- Not consistently immunogenic in children ≤2 years old
- No booster response
- Antibody with less functional activity

Polysaccharide Conjugate Vaccines

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

Haemophilus influenzae type b Conjugate Vaccines

- 3 conjugate vaccines licensed for use in infants as young as 6 weeks of age
- All utilize different carrier proteins
- 2 combination vaccines available that contain Hib vaccine

Haemophilus influenzae type b Conjugate Vaccines

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

Immunogenicity and Vaccine Efficacy

All three 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; HbOC (HibTITER) and PRP-T (ActHIB) require 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
HbOC	Dose 1	Dose 2	Dose 3	Booster
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 <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 Influenza Type b

All three 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 it is necessary to change vaccine type, three doses of any combination constitute the primary series. Any licensed conjugate 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.

***Haemophilus influenzae* type b Vaccine Interchangeability**

- All conjugate Hib vaccines interchangeable for primary series and booster dose
- 3 dose primary series if more than one brand of vaccine used

***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

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

Vaccine	Age at 1st Dose (Months)	Primary Series	Booster
HbOC/PRP-T (HibTITER, 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

HbOC or PRP-T (HibTITER, ActHIB)

Previously unvaccinated infants aged 2–6 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 7–11 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 12–14 months should receive two doses of vaccine, at least 2 months apart. Any previously unvaccinated child aged 15–59 months should receive a single dose of vaccine.

***Haemophilus influenzae* type b Vaccine**
Vaccination Following Invasive Disease

- Children <24 months may not develop protective antibody after invasive disease
- Vaccinate during convalescence
- Complete series for age

***Haemophilus influenzae* type b Vaccine**
Use in Older Children and Adults

- Generally not recommended for persons >59 months of age
- Consider for high-risk persons: asplenia, immunodeficiency, HIV infection, HSCT
- One pediatric dose of any conjugate vaccine

Combination Vaccines Containing Hib

- DTaP—Hib
  —TriHIBit
- Hepatitis B—Hib
  —COMVAX

PRP-OMP (PedvaxHIB)

Unvaccinated children aged 2–11 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 12–14 months should receive two doses of vaccine 2 months apart. Any previously unvaccinated child 15–59 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 **children 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

Two combination vaccines that contain *H. influenzae* type b are available in the United States—a DTaP–Hib combination (TriHIBit, sanofi pasteur), and a hepatitis B–Hib combination (Comvax, Merck). Combination vaccines containing whole-cell pertussis vaccine and Hib are no longer available in the United States.

TriHIBit

TriHIBit was approved 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

- ActHIB reconstituted with Tripedia
- Not approved for the primary series at 2, 4, or 6 months of age
- Approved for the fourth dose of the DTaP and Hib series only
- Primary series Hib doses given as TriHIBit should be disregarded

Because of evidence of reduced immunogenicity of the Hib component when used as a combination, **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 12–15 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 15–59 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.

TriHIBit

- May be used as the booster dose of the Hib series at ≥12 months of age following any Hib vaccine series*
- Should not be used if child has receive no prior Hib doses

*booster dose should follow prior dose by ≥2 months

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

- Hepatitis B-Hib combination
- Use when either or both antigens indicated ≥6 weeks of age
- Not licensed for use if mother HBsAg+
- Spacing and timing rules same as for individual antigens

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/nip/vfc/acip_recs/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.

Adverse Reactions Following Vaccination

***Haemophilus influenzae* type b Vaccine Adverse Reactions**

- Swelling, redness, or pain in 5%-30% of recipients
- Systemic reactions infrequent
- Serious adverse reactions rare

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 Events Reporting System (VAERS) (http://vaers.hhs.gov/).

Contraindications and Precautions to Vaccination

***Haemophilus influenzae* type b Vaccine Adverse Reactions**

- Swelling, redness, or pain in 5%-30% of recipients
- Systemic reactions infrequent
- Serious adverse reactions rare

Vaccination with Hib conjugate vaccine is contraindicated for persons known to have experienced a severe allergic reaction (anaphylaxis) 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 and Comvax are the same as those for its individual component vaccines (i.e., DTaP, Hib, and hepatitis B).

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 workers should report any case of invasive Hib disease to local and state health departments.

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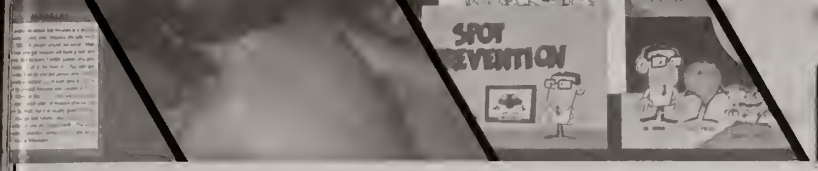


Measles

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 30–40 million cases and 745,000 deaths from measles in 2001.

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 to 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

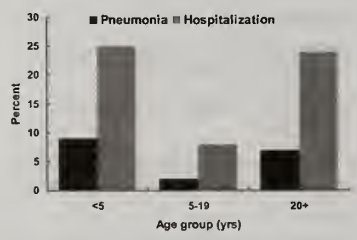
- 2-4 days after prodrome, 14 days after exposure
- Persists 5-6 days
- Begins on face and head
- Maculopapular, becomes confluent
- Fades in order of appearance

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% to 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.

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 Laboratory Diagnosis

- Isolation of measles virus from a clinical specimen (e.g., nasopharynx, urine)
- Significant rise in measles IgG by any standard serologic assay (e.g., EIA, HI)
- Positive serologic test for measles IgM antibody

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

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

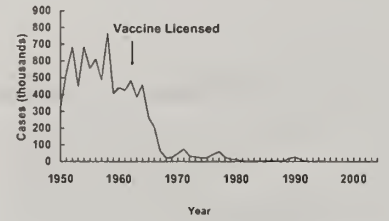
Measles transmission is primarily person to person via large respiratory droplets. Airborne transmission via aerosolized droplet nuclei has been documented in closed areas (e.g., office examination room) for up to 2 hours after a person with measles occupied the area.

Measles Epidemiology

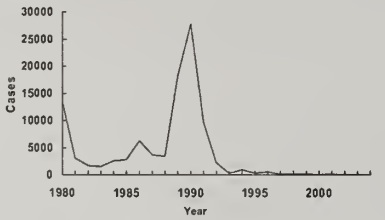
• Reservoir	Human
• Transmission	Respiratory Airborne
• Temporal pattern	Peak in late winter–spring
• Communicability	4 days before to 4 days after rash onset

Measles

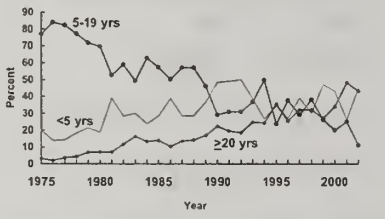
Measles—United States, 1950-2004



Measles—United States, 1980-2004



Age Distribution of Reported Measles, 1975-2002



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 1993-2004

- Record low annual total in 2004 (37 total cases)
- Transmission in the United States interrupted
- 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 measles incidence now being very low in Latin America and the Caribbean. Measles elimination from the Americas appears to be an achievable goal.

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 49 states now require two doses of measles vaccine for school-aged children. As a result, measles outbreaks in school settings are now uncommon.

During the measles resurgence of 1989–1991, outbreaks among preschool-aged children became more prominent. More than 200 outbreaks were reported during each of these years, several of which included more than 1,000 cases. The largest outbreak involving predominantly unvaccinated preschool-aged children was in metropolitan Los Angeles, California. More than 12,000 measles cases were reported during this outbreak, which continued for almost 5 years (1987–1992). The last large outbreak involving preschool-aged children was reported in 1992.

Since 1993, the largest outbreaks of measles have occurred in populations that refuse vaccination for religious or

personal belief reasons, including communities in Utah and Nevada and Christian Scientist schools in Missouri and Illinois. Most outbreaks have involved limited spread from measles imported from outside the United States. The largest outbreak in 2000 involved nine persons in New York.

In 2003, a large measles outbreak occurred in the Republic of the Marshall Islands. Between July 13 and November 7, a total of 826 cases had been reported, with 100 measles-related hospitalizations and 3 deaths. The outbreak affected predominantly preschool-aged children (41% of cases); adults 20 years and older accounted for 24% of cases. The measles virus isolated in this outbreak (H1 genotype) has been documented to circulate in East Asia, particularly Japan, China, and Korea. Factors contributing to this outbreak were low population immunity due to inadequate vaccine coverage, absence of recent transmission of measles virus, and high susceptibility among infants. The outbreak was controlled with aggressive case finding and a large vaccination campaign targeting persons 6 months to 40 years of age.

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, and
- Temperature >101°F (38.3°C), 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 NIP website at http://www.cdc.gov.nip/publications/surv-manual/default.htm).

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

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

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

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 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.

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 as a single-antigen preparation, combined with rubella vaccine, combined with mumps and rubella vaccines (MMR), or combined with mumps, rubella, and varicella vaccine as MMRV (ProQuad). The Advisory Committee on Immunization Practices (ACIP) recommends that a combination vaccine (MMR or MMRV) be used when any of the individual components is indicated (and for MMRV, if the vaccinee is 12 months through 12 years of age). 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.

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 preadolescent health visit at age 11–12 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, rubella, and mumps or other acceptable evidence of immunity to these diseases

Measles (MMR) Vaccine Indications

- All infants ≥12 months of age
- 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

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 Recommendation

- First dose of MMR at 12-15 months
- Second dose of MMR at 4-6 years
- Second dose may be given any time ≥4 weeks after the first dose

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 worker should not provide an immunization record for a patient unless that healthcare worker 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.

At the time of publication of this book (January 2006), ACIP has not made specific recommendations for the use of MMRV (ProQuad). MMRV is approved by the Food and Drug Administration for children 12 months through 12 years of age (that is, until the 13th birthday). However, ACIP has previously stated a preference for use of combination vaccines when one or more component of the combination is indicated and none of the other components are contraindicated. MMRV should not be administered to persons 13 years of age or older.

Adults at Increased Risk of Measles

- College students
- Persons working in medical facilities
- International travelers

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-, rubella-, and mumps-containing vaccine or other acceptable evidence of immunity to these three diseases. With the exception of women who might become pregnant (see Chapter 12, Rubella) and persons who work in medical facilities, birth before 1957 generally can be considered acceptable evidence of immunity to measles, rubella, and mumps.

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, rubella, and mumps 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, rubella, and mumps immunity before entry.

Students who have no documentation of live measles, rubella, or mumps vaccination or other acceptable evidence of measles, rubella, and mumps 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.

Persons who work in **medical facilities** are at higher risk for exposure to measles than the general population. Between 1985 and 1991, at least 795 measles cases occurred in adult healthcare workers, including nurses, physicians, laboratory and radiology technicians, clerks, assistants and students. An overall decline in measles incidence occurred after the 1989–1991 measles resurgence, with a total of 36 cases during 1993–1996 occurring among persons working in medical facilities. However, in 15 of the 75 measles outbreaks reported during 1993–1996, transmission occurred in a medical facility.

All persons who work within medical facilities should have evidence of immunity to measles and rubella. Because any healthcare worker (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 and rubella for healthcare workers born during or after 1957 consists of two doses of a live measles-containing vaccine and at least one dose of a live rubella-containing vaccine. Healthcare workers 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 and rubella immunity, medical facilities should consider recommending a dose of MMR vaccine to

Measles Immunity in Healthcare Personnel

- All persons who work within medical facilities should have evidence of immunity to measles

unvaccinated workers 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.

Measles Vaccine Indications for Revaccination

- Vaccinated before the first birthday
- Vaccinated with killed measles vaccine (KMV)
- Vaccinated with KMV followed by live vaccine <4 months after the last dose of KMV
- Vaccinated before 1968 with an unknown type of vaccine
- Vaccinated with IG in addition to a further attenuated strain or vaccine of unknown type

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 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.

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 5–12 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, rubella, and mumps vaccines may cause fever after vaccination, the measles component of MMR vaccine is most often associated with this adverse reaction. After MMR vaccination, 5%–15% of susceptible persons develop a temperature of 103°F (39.4°C) or higher, usually occurring 7–12 days after vaccination and generally lasting 1–2 days. Most persons with fever are otherwise asymptomatic.

Measles- and rubella-containing vaccines, including MMR, may cause a transient **rash**. Rashes, usually appearing 7–10 days after MMR or measles vaccination, have been reported in approximately 5% of vaccinees.

Rarely, MMR vaccine may cause **thrombocytopenia** (low platelet count) within 2 months after vaccination. Estimates of the frequency of clinically apparent thrombocytopenia from Europe are one case per 30,000 to 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 12, 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.

Contraindications and Precautions to Vaccination

Persons who have experienced a severe allergic reaction (i.e., hives, swelling of the mouth or throat, difficulty breathing, hypotension, shock) following a prior dose of measles vaccine or to a vaccine component (e.g., gelatin, neomycin), 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

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.

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

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.

MMR and other measles-containing vaccines are not recommended for HIV-infected persons with evidence of severe immunosuppression (see table), primarily because of a report of measles pneumonitis in a recipient of measles vaccine who had severe HIV-related immunosuppression.

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%

Persons with **moderate or severe acute illness** should not be vaccinated until the illness has improved or resolved. 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. One recent study suggested that seroconversion after measles vaccine was reduced in children with upper respiratory infections. However, multiple previous and subsequent studies have not confirmed this finding.

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 7–11 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** 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 thrombocytopenia 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 testing (PPD) is not a prerequisite for vaccination with MMR or other measles-containing vaccine. PPD testing 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 PPD in a person infected with *Mycobacterium tuberculosis*. If tuberculin skin testing is needed at the same time as administration of measles-containing vaccine, PPD and vaccine can be administered at the same visit. Simultaneously administering PPD and measles-containing vaccine does not interfere with reading the PPD result at 48–72 hours and ensures that the person has received measles vaccine. If the measles-containing vaccine has been administered recently, PPD screening should be delayed at least 4 weeks after vaccination. A delay in administering PPD will remove the concern of any theoretical suppression of PPD reactivity from the vaccine. PPD 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.

PPD and Measles Vaccine

- **Apply PPD at same visit as MMR**
- **Delay PPD ≥4 weeks if MMR given first**
- **Apply PPD first—give MMR when skin test read**

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. MMRV may not be stored at refrigerator temperature at any time.

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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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. Outbreaks of mumps have been reported among military personnel as recently as 1986.

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 12–25 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 14–18 days (range, 14–25 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%–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

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)

As many as 20% of mumps infections are asymptomatic. An additional 40%–50% may have only nonspecific or primarily respiratory symptoms.

Complications

Central nervous system (CNS) involvement in the form of aseptic meningitis is common, occurring asymptomatically (inflammatory cells in cerebrospinal fluid) in 50%–60% of patients. Symptomatic meningitis (headache, stiff neck) occurs in up to 15% of patients and resolves without sequelae in 3–10 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 clinical samples acceptable for mumps virus isolation are throat or nasopharyngeal swabs, urine, and fluid collected from the buccal cavity. The buccal cavity is the space between the cheek and teeth. The parotid duct drains in this space near the upper rear molars. Fluid from this area may yield the best viral sample, particularly when the parotid gland area just below the ear is massaged for 30 seconds prior to collection of secretions. Virus may be isolated from the buccal mucosa or urine from 7 days before until 9 days after onset of parotitis. 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.

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

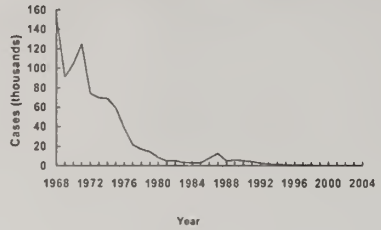
Mumps incidence peaks predominantly in late winter and spring, but the disease has been reported throughout the year.

Mumps Epidemiology

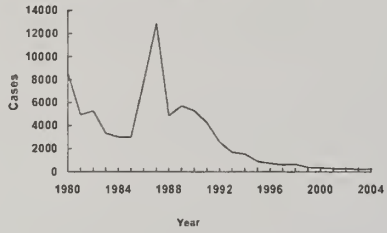
• Reservoir	Human Asymptomatic infections may transmit
• Transmission	Respiratory drop nuclei
• Temporal pattern	Peak in late winter and spring
• Communicability	Three days before to four days after onset of active disease

Mumps

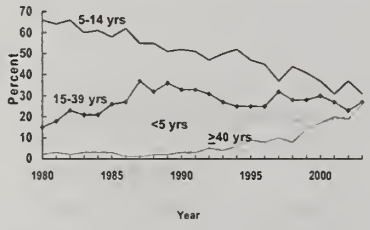
Mumps—United States, 1968-2004



Mumps—United States, 1980-2004



Mumps—United States, 1980-2003
Age Distribution of Reported Cases



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. As more children, adolescents, and adults received two doses of measles-mumps-rubella (MMR) vaccine, the number of reported cases of mumps has continued to decrease. Because many reported cases are not confirmed by laboratory testing, it is likely that many of the cases lacking laboratory confirmation are, in fact, not due to infection with mumps virus. Experience in states that have conducted more complete laboratory testing for confirmation suggests that case investigation combined with appropriate laboratory testing will result in many suspected cases being discarded and a resulting decrease in reported mumps morbidity. Laboratory confirmation helps ensure that only true mumps cases are reported.

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%–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 without other apparent cause.

Mumps Clinical Case Definition

- Acute onset of unilateral or bilateral tender, self-limited swelling of the parotid or other salivary gland lasting >2 days 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 as a single-antigen preparation, combined with rubella vaccine, combined with measles and rubella vaccines, or combined with mumps, rubella, and varicella vaccine as MMRV (ProQuad). The Advisory Committee on Immunization Practices (ACIP) recommends that combined measles-mumps-rubella vaccine be used when any of the individual components is indicated (and for MMRV, if the vaccinee is 12 months through 12 years of age). 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	≥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. Clinical efficacy has been estimated to be 95% (range, 90%–97%). 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

At least one dose of mumps-containing vaccine is routinely recommended for all children and for all persons born during or after 1957. The first dose of mumps-containing vaccine should

Mumps (MMR) Vaccine Indications

- All infants ≥12 months of age
- Susceptible adolescents and adults without documented evidence of immunity

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.

A second dose of MMR is recommended to produce immunity to measles 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. 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 of MMR 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 be given routinely at age 4–6 years, before a child enters kindergarten or first grade. The adolescent health visit at age 11–12 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.

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-, rubella-, and mumps-containing vaccine or other acceptable evidence of immunity to these three diseases. Some adults at high risk of measles exposure may require a second dose of measles vaccine. This second dose should be administered as combined MMR vaccine (see Chapter 10, Measles, for details).

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 worker should not provide an immunization record for a patient unless that healthcare worker 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.

At the time of publication of this book (January 2006), ACIP has not made specific recommendations for the use of MMRV (ProQuad). MMRV is approved by the Food and Drug Administration for children 12 months through 12 years of age (that is, until the 13th birthday). However, ACIP has previously stated a preference for use of combination vaccines when one or more component of the combination is indicated and none of the other components are contraindicated. 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.

Mumps Immunity

- Born before 1957
- Serologic evidence of mumps immunity
- Documentation of physician-diagnosed mumps
- Documentation of adequate vaccination

Live mumps vaccine was not used routinely before 1977, and the peak incidence of disease was among 5- to 9-year-olds before the vaccine was introduced. Most persons born before 1957 are likely to have been infected naturally between 1957 and 1977. As a result, persons born before 1957 generally may be considered to be immune, even if they did not have clinically recognizable mumps disease. However, as with measles and rubella, this 1957 cutoff date for susceptibility is arbitrary, and vaccination with MMR should be considered during mumps outbreaks for persons born before 1957 who may be exposed to mumps and may be nonimmune. Laboratory testing for mumps susceptibility before vaccination is not necessary.

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.

Adverse Reactions Following Vaccination

Mumps is a very safe vaccine. 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

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

field trials. Subsequently, **parotitis** and **fever** have been reported rarely. A few cases of orchitis (all suspect) also have been reported.

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.

Contraindications and Precautions to Vaccination

Persons who have experienced a severe allergic reaction (i.e., hives, swelling of the mouth or throat, difficulty breathing, hypotension, shock) following a prior dose of mumps vaccine or to a vaccine component (e.g., gelatin, neomycin), 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,

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

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 10, 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 resolved. Minor illness (e.g., otitis media, mild upper respiratory infections), concurrent 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.

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. MMRV may not be stored at refrigerator temperature at any time.

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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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 reported recognition of congenital rubella syndrome (CRS).

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 was first isolated in 1962 by Parkman and Weller. 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 5–7 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 12–23 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 1–5 day prodrome with low-grade fever, malaise, lymphadenopathy, and upper respiratory symptoms preceding the rash. The rash of rubella is maculopapular and occurs 14-17 days after exposure. 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

rash usually occurs initially on the 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 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 are not common, but they tend to 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**.

Rubella Complications

Arthralgia or arthritis	
adult female	up to 70%
children	rare
Thrombocytopenic purpura	1/3,000 cases
Encephalitis	1/6,000 cases
Neuritis	rare
Orchitis	rare

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

Epidemic Rubella – United States, 1964-1965

- 12.5 million rubella cases
- 2,000 encephalitis cases
- 11,250 abortions (surgical/spontaneous)
- 2,100 neonatal deaths
- 20,000 CRS cases
  - –deaf - 11,600
  - –blind - 3,580
  - –mentally retarded - 1,800

emotional toll on the families involved. The estimated lifetime cost of one case of CRS today is estimated to be in excess of $200,000.

Infection with rubella virus can be disastrous 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.

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. A state laboratory or CDC should be consulted for details of viral isolation.

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.

Hemagglutination inhibition (HI) test was once the "standard" and most commonly used technique. It is sensitive and simple to perform and allows for either screening or diagnosis (if paired acute- and convalescent-phase sera are tested). A fourfold rise or greater in HI-derived antibody titer in paired sera is diagnostic of recent infection. The test may be modified to detect rubella-specific IgM antibody indicative of primary infection.

Immunofluorescent antibody assay (IFA) is a rapid and sensitive assay. Commercial assays for both IgG and IgM are available in the United States. Care must be taken with the IgM assay to avoid false-positive results due to complexes with rheumatoid antibody.

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 is erupting, but virus may be shed from 7 days before to 5–7 days or more after rash onset.

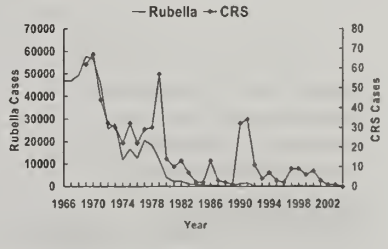
Infants with CRS shed large quantities of virus from body secretions for up to 1 year and can therefore transmit rubella to persons caring for them who are susceptible to the disease.

Rubella Epidemiology

• Reservoir	Human
• Transmission	Respiratory Subclinical cases may transmit
• Temporal pattern	Peak in late winter and spring
• Communicability	7 days before to 5-7 days after rash onset Infants with CRS may shed virus for a year or more

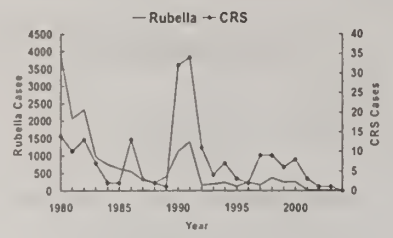
Secular Trends in the United States
Rubella and congenital rubella syndrome became nationally notifiable diseases in 1966. The largest annual total of cases of rubella in the United States was in 1969, when 57,686 cases were reported (58 cases per 100,000 population). Following vaccine licensure in 1969, 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.

Rubella - United States, 1966-2004

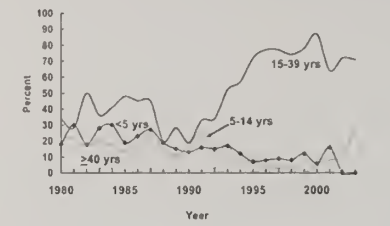


Rubella

Rubella - United States, 1980-2004



Rubella - United States, 1980-2003
Age Distribution of Reported Cases



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, most born in Latin America

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

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 Immunization Program. 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 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, most 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

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 January 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.

Rubella

Rubella Vaccine

• Composition	Live virus (RA 27/3 strain)
• Efficacy	95% (Range, 90%-97%)
• Duration of Immunity	Lifelong
• Schedule	≥1 Dose

• Should be administered with measles and mumps as MMR or with measles, mumps and varicella as MMRV

Rubella Vaccine (MMR) Indications

- All infants >12 months of age
- Susceptible adolescents and adults without documented evidence of rubella immunity
- Emphasis on nonpregnant women of childbearing age, particularly those born outside the 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 is available as a single-antigen preparation, combined with mumps vaccine, combined with measles and mumps vaccines as MMR, or combined with mumps, rubella, 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 (and for MMRV, if the vaccinee is 12 months through 12 years of age). Use of single-antigen rubella vaccine is not routinely 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

At least one dose of rubella vaccine, as combination MMR

(or MMRV) vaccine, is routinely recommended for all children. 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 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 to measles 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 4–6 years, before a child enters kindergarten or first grade. The adolescent health visit at age 11–12 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.

All older children not previously immunized should receive at least one dose of rubella vaccine as MMR.

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-, rubella-, and mumps-containing vaccine or other acceptable evidence of immunity to these three diseases. Some adults at high risk of measles exposure may require a second dose of measles vaccine. 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 worker should not provide an immunization record for a patient unless that healthcare worker 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.

At the time of publication of this book (January 2006) ACIP has not made specific recommendations for the use of MMRV (ProQuad). MMRV is approved by the Food and Drug Administration for children 12 months through 12 years of age (that is, until the 13th birthday). However, ACIP has previously stated a preference for use of combination vaccines when one or more component of the combination is indicated and none of the other components are contraindicated. 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.

Rubella Immunity

- **Documentation of one dose of rubella-containing vaccine on or after the first birthday**
- **Serologic evidence of immunity**
- **Birth before 1957 (except women of childbearing age)**

Rubella Immunity

- **Birth before 1957 is not acceptable evidence of rubella immunity for women who might become pregnant**
- **Only serology or documented vaccination should be accepted**

Healthcare workers born before 1957 also should not be presumed to be immune. Medical facilities should consider recommending a dose of MMR vaccine to unvaccinated healthcare workers 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 workers who could become pregnant, including those born before 1957. This recommendation is based on serologic studies which indicate that among hospital workers born before 1957, 5%–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.

Adverse Reactions Following Vaccination

Rubella is a very safe vaccine. 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 susceptable adult women
- Acute arthritis-like signs and symptoms occurs in about 10%
- Rare reports of chronic or persistent symptoms
- Population-based studies have not confirmed association

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.

Contraindications and Precautions to Vaccination

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

Persons who have experienced a **severe allergic reaction** (i.e., hives, swelling of the mouth or throat, difficulty breathing, hypotension, shock) following a prior dose of rubella vaccine or to a vaccine component (e.g., gelatin, neomycin), should generally not be vaccinated with MMR.

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 (see next section), 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.

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.

Vaccination of Women of Childbearing Age

- **Ask if pregnant or likely to become so in next 4 weeks**
- **Exclude those who say "yes"**
- **For others**
  - **explain theoretical risks**
  - **vaccinate**

Vaccination in Pregnancy Study 1971-1989

- 321 women vaccinated
- 324 live births
- No observed CRS
- 95% confidence limits 0%-1.2%

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 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 colder at all times. MMRV must be stored at an average temperature of 5°F (-15°C) or colder at all times. MMRV may not be stored at refrigerator temperature at any time.

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

Although the number of CRS cases is low, rubella transmission continues to occur, and increased in 1989 and 1990. The elimination of CRS will require several interventions:

- Achievement and maintenance of high immunization levels.
- Intensive surveillance of rubella and CRS.
- Prompt outbreak control when rubella occurs.

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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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 healthy children and adults in the United States in March 1995.

Varicella

- Acute viral illness
- Zoster described in premedieval times
- Varicella not differentiated from smallpox until end of 19th century
- Infectious nature demonstrated in 1875

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 outside the infected host.

Varicella Zoster Virus

- Herpesvirus (DNA)
- Primary infection results in varicella (chickenpox)
- Recurrent infection results in herpes zoster (shingles)
- Short survival in 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 4–6 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 following the appearance of the rash.

Varicella Pathogenesis

- Respiratory transmission of virus
- Replication in nasopharynx and regional lymph nodes
- Repeated episodes of viremia
- Multiple tissues, including sensory ganglia, infected during viremia

Clinical Features

The **incubation period** is from 14 to 16 days from exposure, with a range of 10–21 days. The incubation period may be prolonged in immunocompromised patients and those who have received varicella zoster immune globulin (VZIG). The incubation period may be up to 28 days after receipt of VZIG.

Varicella Clinical Features

- Incubation period 14-16 days (range 10-21 days)
- Mild prodrome for 1-2 days
- Generally appear first on head; most concentrated on trunk
- Successive crops (2-4 days) of pruritic vesicles

Varicella

Primary Infection (Chickenpox)

A mild **prodrome** may precede the onset of a rash. Adults may have 1–2 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 scalp, then on the trunk, and then the extremities, with the highest concentration of lesions 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 1–4 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 200–500 lesions in 2 to 4 successive crops.

The **clinical course** in healthy children is generally mild, with malaise, pruritus (itching), and fever up to 102°F for 2–3 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 may also 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 this 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, 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 dermatome supplied by a dorsal root

Herpes Zoster

- Reactivation of varicella zoster virus
- Associated with:
  - aging
  - immunosuppression
  - intrauterine exposure
  - varicella at <18 months of age

or extramedullary cranial nerve sensory ganglion. Most often, this involves the trunk or the area of the fifth cranial nerve. Two to four days prior to the eruption, there may be pain and paresthesia in the segment involved. There are few systemic symptoms. Postherpetic neuralgia, or pain in the area of the recurrence which persists after the lesions have resolved, is a distressing complication of zoster, with no adequate therapy currently available. Postherpetic neuralgia may last as long as a year after the episode of zoster. Ocular nerve and other organ involvement with zoster can occur, often with severe sequelae.

Complications

Acute varicella is generally mild and self-limited, but it may be associated with complications. The most common complications of varicella include **secondary bacterial infections** of skin lesions, dehydration, pneumonia, and central nervous system (CNS) involvement. 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.

Varicella Complications

- Bacterial infection of lesions
- CNS manifestations
- Pneumonia (rare in children)
- Hospitalization ~3 per 1,000 cases
- Death ~1 per 60,000 cases

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.

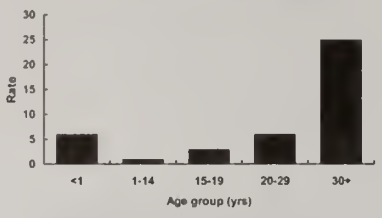
Reye syndrome is an unusual complication of varicella and influenza and occurs almost exclusively in children who take aspirin during the acute illness. The etiology of Reye syndrome is unknown. There has been a dramatic decrease in the incidence of Reye syndrome during the past decade, presumably related to decreased use of aspirin by children.

Rare complications of varicella include aseptic meningitis, transverse myelitis, Guillain-Barré syndrome, thrombocytopenia, hemorrhagic varicella, purpura fulminans, glomerulonephritis, myocarditis, arthritis, orchitis, uveitis, iritis, and clinical 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 immunologically normal children and adults.

Varicella Fatality Rate in Healthy Persons



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 varicella 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.

Groups at Increased Risk of Complications of Varicella

- Healthy adults
- Immunocompromised persons
- Newborns of mothers with rash onset within 5 days before to 48 hours after delivery

Immunocompromised persons have a high risk of acquiring serious varicella infection and 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.

Perinatal Infection

The onset of maternal varicella from 5 days before to 48 hours 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.

Congenital Varicella Syndrome

- Results from maternal infection during pregnancy
- Period of risk may extend through first 20 weeks of pregnancy
- Low birth weight, atrophy of extremity with skin scarring, eye and neurologic abnormalities
- Risk appears to be small (< 2%)

Congenital VZV Infection

Primary 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 during the first trimester 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. Intrauterine infection with VZV, particularly after 20 weeks' gestation, is associated with zoster in those infants at an earlier age; the exact risk is unknown.

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 such, the need for laboratory confirmation of varicella is on the increase.

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 zoster virus identification. Rapid 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 more widely available than in the past 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/nip/publications/surv-manual/

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 and 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 email vzvlab@cdc.gov for details about collecting and submitting specimens for testing.

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

Epidemiology

Occurrence

Varicella and herpes zoster occur worldwide. Some data suggest that varicella infection is less common in childhood in tropical areas, where chickenpox occurs more commonly among adults. 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.

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.

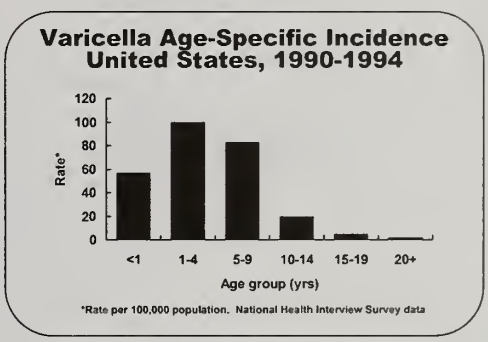
Varicella is highly contagious. It is less contagious than measles, but more so than mumps and rubella. Secondary attack rates among susceptible household contacts of persons with varicella are as high as 90% (that is, 9 of 10 susceptible household contacts of persons with varicella will become infected).

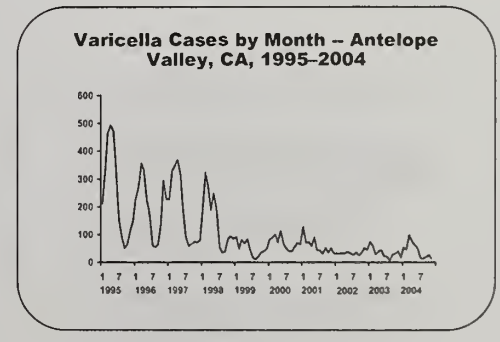
Secular Trends in the United States

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.

In the prevaccine era, 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





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

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.

Herpes Zoster

Herpes zoster is not a notifiable condition. An estimated 300,000 episodes of zoster occur annually. Ninety-five percent of these episodes are first occurrences, and 5% are recurrences. The risk of zoster increases with increasing age. By age 80, almost 15% of persons will have experienced at least one episode of zoster.

Varicella Vaccine

Varicella Vaccine

- Composition: Live virus (Oka/Merck strain)
- Efficacy: 95% (Range, 65%-100%)
- Duration of Immunity: >7 years
- Schedule: 1 Dose (<13 years of age)

May be administered simultaneously with measles, mumps, and rubella (MMR) vaccine

11 13

Characteristics

Varicella zoster vaccine 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. 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 does not contain egg, ovalbumin, or preservative.

On September 6, 2005, the Food and Drug Administration licensed a combined live attenuated measles-mumps-rubella and varicella (MMRV) vaccine (ProQuad) 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 3.99 $\log_{10}$ plaque-forming units (PFU) versus 1,350 PFU (~3.13 $\log_{10}$), respectively.

Immunogenicity and Vaccine Efficacy

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 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%–90% against infection, and 85%–95% against moderate or severe disease. In field conditions, varicella vaccine is 80%–85% effective against infection and more than 95% effective against severe disease.

Among healthy adolescents and adults, an average of 78% develop antibody after one dose, and 99% develop antibody after a second dose given 4 to 8 weeks later. Antibody has persisted for at least 1 year in 97% of vaccinees after the second dose given 4 to 8 weeks after the first dose. Studies on the persistence of antibody and clinical efficacy in both children and adults are ongoing.

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.

Immunity appears to be long-lasting, and is probably permanent in the majority of vaccinees. Breakthrough infection (i.e., varicella disease in a vaccinated person) 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 younger age (i.e., younger than 15 months) risk factors for breakthrough varicella. However, because of the inconsistency of these data, ACIP has not changed its recommendations for use of varicella vaccine.

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 in two health maintenance organizations found that children who received varicella vaccine less than 30 days after MMR vaccination had a 2.5-fold increased risk of

Breakthrough Infection

- Immunity appears to be long-lasting for most recipients
- Breakthrough disease much milder than in unvaccinated persons
- No consistent evidence that risk of breakthrough infection increases with time since vaccination

Breakthrough Infection

- Retrospective cohort study of 115,000 children vaccinated in 2 HMOs during January 1995 through December 1999
- Risk of breakthrough varicella 2.5 times higher if varicella vaccine administered less than 30 days following MMR
- No increased risk if varicella vaccine given simultaneously or more than 30 days after MMR

MMWR 2001;50(47):1058-61

breakthrough varicella compared with those who received varicella vaccine before, simultaneously with, or more than 30 days after MMR. Inactivated vaccines (DTaP, Hib, IPV, and hepatitis B) and OPV did not increase the risk of breakthrough varicella if administered less than 30 days prior to varicella vaccine.

Varicella Vaccine Recommendations
Children

- Routine vaccination at 12-18 months of age
- Recommended for all children without evidence of varicella immunity by the 13th birthday

Vaccination Schedule and Use

Varicella virus vaccine is recommended for all children without contraindications at 12–18 months of age. The vaccine may be given to all children at this age regardless of prior history of varicella. However, vaccination is not necessary for children with reliable histories of chickenpox.

Varicella vaccine is also recommended for all children without evidence of varicella immunity (see below) by the 13th birthday. Children who have not been vaccinated previously and who do not have a reliable history of chickenpox are considered susceptible. Efforts should be made to ensure varicella immunity by this age, because after 13 years of age varicella disease is more severe, complications are more frequent, and two doses of vaccine are required.

MMRV vaccine is indicated for simultaneous vaccination against measles, mumps, rubella and varicella in children 12 months through 12 years of age; persons outside of this age group should not receive this vaccine. MMRV vaccine can reduce the number of injections when administered to children 12 months through 12 years of age for whom a) the first dose of MMR and varicella vaccines are indicated, and b) the second dose of MMR and either the first or the second dose (i.e., during varicella outbreaks) of varicella vaccines are indicated. Use of licensed combination vaccines, such as MMRV vaccine, is preferred to separate injection of their equivalent component vaccines. When used, MMRV vaccine should be administered on or after the first birthday, preferably as soon as the child becomes eligible for vaccination.

Varicella vaccine should be administered subcutaneously. It 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 12–18 months of age.

Children with a reliable 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 who do not have evidence of varicella immunity**. Approximately 80% of adolescents and adults respond to a single dose of varicella vaccine. In contrast, at least 97% of healthy children will develop detectable antibody after a single dose. As a result, persons 13 years of age and older should receive **two doses** of varicella vaccine separated by 4–8 weeks. If there is a lapse of more than 8 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.

Vaccination of Persons 13 Years of Age and Older

Varicella vaccine was previously recommended for persons 13 years of age and older without evidence of immunity who have close contact with persons at high risk for severe disease (e.g., healthcare workers and family contacts of immunocompromised persons) or who are at high risk for exposure or transmission. The ACIP now recommends that all other persons in this age group without evidence of immunity be vaccinated with two doses of varicella vaccine administered 4–8 weeks apart. The vaccine may be offered during routine healthcare visits.

The ACIP recommends that **all healthcare workers** be immune to varicella, either from a reliable history of varicella disease or from vaccination. 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.

Varicella Vaccine Recommendations Adolescents and Adults

- All persons ≥13 years of age without evidence of varicella immunity
- Two doses separated by 4-8 weeks
- Do not repeat first dose because of extended interval between doses

Vaccination of Healthcare Workers

- Recommended for all susceptible healthcare workers
- Prevaccination serologic screening probably cost-effective
- Postvaccination testing not necessary or recommended

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 worker is exposed to VZV, the employee should be monitored daily from day 10 to day 21 after exposure through the employee health program or infection control nurse to determine clinical status (screen for fever, skin lesions, and systemic symptoms). Of note, persons with varicella may be infectious starting 2 days before rash onset. In addition, the healthcare worker should 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. Healthcare institutions may establish protocols and recommendations for screening and vaccinating healthcare workers and for management of healthcare workers following exposures in the workplace.

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, below), and the benefits of vaccinating susceptible healthcare workers 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, institutions may wish to consider precautions 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).

Varicella Immunity

- Written documentation of age-appropriate vaccination
- Born in the U.S. before 1966
- History of typical varicella disease among:
  - —non-U.S. born persons born before 1966
  - —all persons born during 1966-1997
- History of herpes zoster based on healthcare provider diagnosis
- Laboratory evidence of immunity or laboratory confirmation of disease

Varicella Immunity

In 2005 the ACIP approved a revised definition for evidence of immunity to varicella. Evidence of immunity to varicella includes any of the following:

1) Written documentation of age-appropriate vaccination;
2) Born in the United States before 1966;
3) History of varicella disease based on healthcare provider diagnosis or self or parental report of typical varicella disease for non-U.S.-born persons born before 1966, and all persons born during 1966–1997. For persons reporting a history of atypical mild disease, healthcare providers should seek either a) an epidemiologic link to a typical varicella case (e.g., case occurred in the context of an outbreak or patient had household exposure in the previous 3 weeks), or b) evidence of laboratory confirmation, if it was performed at the time of acute disease. When such documentation is lacking, persons should not be considered as having a valid history of disease because other diseases may mimic mild atypical varicella.

For persons born during or after 1998, history of disease is no longer considered as evidence of immunity, unless the illness was laboratory confirmed.

4) History of herpes zoster based on healthcare provider diagnosis; or
5) Laboratory evidence of immunity or laboratory confirmation of disease.

Postexposure Prophylaxis

Data from the United States and Japan in a variety of settings indicate that varicella vaccine is 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 Vaccine Postexposure Prophylaxis

- Varicella vaccine is recommended for use in persons without evidence of varicella immunity after exposure to varicella
  - —70%-100% effective if given within 72 hours of exposure
  - —not effective if >5 days but will produce immunity if not infected

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. Varicella vaccine should be used for outbreak control by advising exposed persons without evidence of varicella immunity to contact their healthcare providers for vaccination or by offering vaccination through the health department. The ACIP now recommends a second dose of varicella vaccine for outbreak control. During a varicella outbreak, persons who have received one dose of varicella vaccine should, resources permitting, 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).

Adverse Reactions Following Vaccination

The most common adverse reactions following varicella vaccine are those at the **injection site**, such as pain, soreness, redness, 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 reactions are generally mild and self-limited. A varicella-like rash at injection site is reported by

Varicella Vaccine Adverse Reactions

- Injection site complaints
  19% (children)
  24% (adolescents and adults)
- Rash – 3%-4%
  - —may be maculopapular rather than vesicular
  - —average 5 lesions
- Systemic reactions not common

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 a median of five lesions. Most of these generalized rashes occur within 3 weeks and most are maculopapular.

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 intercurrent 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.

Zoster Following Vaccination

- Most cases in children
- Risk from vaccine virus less than from wild virus
- Usually a mild illness without complications

Contraindications and Precautions to Vaccination

Contraindications and precautions to varicella vaccine are similar to those for other live attenuated vaccines. Persons with a **severe allergic reaction to a vaccine component or following a prior dose of vaccine** should not receive varicella vaccine. Varicella vaccine contains minute amounts of neomycin and gelatin but does not contain egg protein or preservatives.

Varicella Vaccine Contraindications and Precautions

- Severe allergic reaction to vaccine component or following a prior dose
- Immunosuppression
- Pregnancy
- Moderate or severe acute illness
- Recent blood product

Persons with **immunosuppression** due to 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, replacement, or aerosolized steroid preparations is not a contraindication to varicella vaccination. Persons whose immunosuppressive therapy with steroids has been discontinued for 1 month (3 months for chemotherapy) may be vaccinated.

Varicella Vaccine Use in Immunocompromised Persons

- Most immunocompromised persons should not be vaccinated
- Vaccinate persons with isolated humoral immunodeficiency
- Consider varicella vaccination for asymptomatic HIV-infected children with CD4% $\geq$15% (CDC class A1 and N1)

Varicella vaccine should not be administered to persons with cellular immunodeficiency. However, in 1999, ACIP recommended that persons with isolated humoral immunodeficiency (e.g., hypogammaglobulinemia and agammaglobulinemia) should be vaccinated.

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. However, vaccination should be considered for children with asymptomatic or mildly symptomatic HIV infection (CDC class N1 or A1, age-specific CD4+ T-lymphocyte percentage of 15% or higher). These children should receive two doses of varicella vaccine with a 3-month interval between doses. Because persons with impaired cellular immunity are potentially at greater risk for complications after vaccination with a live vaccine, these vaccinees should be encouraged to return for evaluation if they experience a postvaccination varicella-like rash.

Women known to be **pregnant** or attempting to become pregnant should not receive varicella vaccine. To date, no adverse outcomes of pregnancy or in a fetus have been reported among women inadvertently vaccinated shortly before or during pregnancy. Although the manufacturer's package insert states otherwise, ACIP and the American Academy of Pediatrics recommend that pregnancy be avoided for 1 month following receipt of varicella vaccine.

The ACIP now 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 4–8 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.

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.

Transmission of Varicella Vaccine Virus

- Transmission of vaccine virus not common
- Asymptomatic seroconversion may occur in contacts without evidence of varicella immunity
- Risk of transmission increased if vaccinee develops rash

Varicella Vaccination in Pregnancy Registry

800.986.8999

The effect of the administration of **antibody-containing blood products** (e.g., immune globulin, whole blood or packed red blood cells, intravenous immune globulin, or varicella zoster immune globulin [VZIG]) 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 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, for additional details). Immune globulin or VZIG 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 vaccine because of the association between aspirin use and Reye syndrome following chickenpox.

Transmission of Varicella Vaccine Virus

Available data suggest that transmission of vaccine virus is a rare event. Instances of suspected secondary transmission of vaccine virus have been reported. However, 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. However, 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.

Vaccine Storage and Handling

Varicella vaccine is very fragile and must be handled with extreme care. To maintain potency, the lyophilized vaccine 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 designed to maintain temperatures as low as -4°F (-20°C) and are acceptable for storage of the

Vaccine Storage and Handling
Varicella Vaccine

- **Store frozen at 5°F (-15°C) or lower**
- **Store diluent at room temperature or refrigerate**
- **Discard if not used within 30 minutes of reconstitution**

vaccine. 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, the vaccine must be used immediately to minimize loss of potency. The vaccine must be discarded if not used within 30 minutes of reconstitution.

If varicella vaccine is inadvertently placed in the refrigerator, or if unreconstituted vaccine is left at room temperature for a short time, it may still be potent enough to use. Mishandled vaccine should be clearly marked and replaced in the freezer separate from properly handled vaccine. After the vaccine is stored this way, the manufacturer must be contacted for recommendations before any of the mishandled vaccine is used. The Merck Vaccine Division varicella information telephone number is 800-9VARIVAX (800-982-7482). If the vaccine has been kept cold or has been exposed to room temperature for a very short time, the manufacturer may recommend that the expiration date be shortened and that the vaccine be used as quickly as possible. Mishandled vaccine should never be destroyed until the manufacturer has been consulted.

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 high-quality 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. The vaccine may be kept at refrigerator temperature for up to 72 hours, but it must then be discarded if not used. The vaccine should not be refrozen.

MMRV must be shipped to maintain a temperature of -4°F (-20°C) or colder at all times. It must be stored at an average temperature of 5°F (-15°C) or colder at all times. MMRV may not be stored at refrigerator temperature at any time. MMRV must be administered within 30 minutes of reconstitution.

Varicella Vaccine Information

800-9VARIVAX

Vaccine Storage and Handling MMRV

- Must be shipped to maintain a temperature of ≤- 4°F (-20°C) at all times
- Must be stored at an average temperature of ≤5°F (-15°C) at all times
- May NOT be stored at refrigerator temperature at any time
- Must be administered within 30 minutes of reconstitution

Varicella Zoster Immune Globulin (VZIG)

- May modify or prevent disease if given within 96 hours after exposure
- Indications
  - —immunocompromised persons
  - —newborn of mothers with onset 5 days before to 48 hours after delivery
  - —premature infants with postnatal exposure
  - —susceptible adults and pregnant women
- Supply of VZIG limited – may use IVIG or acyclovir (see NIP website for details)

Varicella Zoster Immune Globulin

VZIG is a human blood product that contains high titers of varicella zoster virus antibody. It was licensed in 1981 and is available from the distributor (FFF Enterprises, Inc., Temecula, CA) by calling 800-843-7477. If administered within 96 hours of exposure, VZIG can modify or prevent clinical varicella and prevent complications or death, especially in susceptible immunocompromised individuals.

The decision to administer VZIG should be based on whether the patient does not have evidence of varicella immunity, either by having a negative history of chickenpox or by lacking documentation of vaccination; whether the exposure is likely to result in infection; and, most importantly, whether the patient is at greater risk of complications than the general population. VZIG is expensive ($400–$500 for the maximum dose for an adult) and provides only temporary protection.

VZIG is indicated for use in persons without evidence of varicella immunity who are at high risk for complications and who have had a significant exposure (continuous household contact; playmate contact of more than an hour; hospital contact in the same 2- to 4-bed room; or prolonged direct contact) to a person with varicella. It is most commonly used for postexposure prophylaxis of immunocompromised children (immune deficiencies, neoplastic disease, or receiving immunosuppressive therapy), and newborns of mothers with varicella onset 5 days before to 48 hours after delivery. It is also recommended for premature infants with postnatal exposure, including those born at less than 28 weeks' gestation or who are less than 1,000 gram birth weight (who may not have received adequate maternal antibody regardless of whether the mother is immune), or premature infants whose mother is not immune to varicella.

Healthy and immunocompromised adults and pregnant women are at increased risk of complications of varicella. VZIG should be considered if such persons do not have evidence of varicella immunity. There is no evidence that VZIG will prevent congenital varicella if given as postexposure prophylaxis to a pregnant woman.

VZIG is supplied in vials containing 125 or 625 units. The recommended dose considered likely to prevent or modify varicella is 125 units per 10 kilograms of body weight, up to a maximum of 625 units, or five vials. Higher doses can be considered for immunosuppressed persons. VZIG is given intramuscularly and must never be given intravenously. It should be given within 96 hours of exposure, preferably as soon as possible. The administration of VZIG may prolong the incubation period of varicella to 28 days or longer postexposure.

More detailed information on the evaluation of a person exposed to varicella and the use of VZIG can be found in the varicella ACIP statement (available at http://www.cdc.gov/nip/publications/acip-list.htm).

As of December 2005, because of discontinuation of the product by the manufacturer, the distributor has limited supplies of VZIG (625-unit vials only) that are expected to last until only until early 2006. In light of the VZIG shortage, the ACIP approved recommendations for postexposure prophylaxis of severe varicella during a VZIG shortage.

For postexposure prophylaxis of varicella of patients without evidence of immunity who are at high risk for severe disease and complications, VZIG is the preferred method. If VZIG is not available, intravenous immune globulin (IGIV) can be used. The recommendation for the use of IGIV is based on "best judgment of experts" and is supported by reports comparing VZV IgG antibody titers measured in both IGIV and VZIG preparations and patients given IGIV and VZIG. Licensed IGIV preparations contain anti-varicella antibodies at varying levels. No clinical data demonstrating effectiveness of IGIV for postexposure prophylaxis of varicella are available.

Indications for the use of IGIV include 1) immunocompromised patients; 2) neonates whose mothers develop signs and symptoms of varicella around the time of delivery (5 days before to 2 days after); 3) premature infants exposed during the neonatal period whose mothers do not have evidence of immunity; 4) premature infants who are less than 28 weeks' gestation or who weigh less than 1,000 grams at birth and who are exposed during the neonatal period, regardless of maternal history of varicella; or 5) pregnant women. Clinicians may choose either to administer IGIV or closely monitor the pregnant woman for signs and symptoms of varicella and institute treatment with acyclovir if illness develops.

Based on experience with VZIG, IGIV could be expected to provide maximum benefit when administered as soon as possible after the exposure and may be effective if administered as late as 96 hours after exposure. IGIV should be administered intravenously as directed by the manufacturer. The recommended IGIV dose for postexposure prophylaxis of varicella is 400 mg/kg. This dose is estimated to yield VZV antibody titers in the recipients comparable to those produced by the recommended VZIG dose (22.5 mg/kg).

The antiviral drug acyclovir is also recommended by some experts for postexposure prophylaxis in a dosage of 40–80 mg/kg/day for children and 800 mg five times/day for adults. The recommendation is for administration beginning from day 7 to day 10 after exposure and for a total of 7 days of therapy.

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Varicella Antiviral Therapy

- Not recommended for routine use among otherwise healthy infants and children with varicella
- Consider for persons age >13 years
- Consider for persons with chronic cutaneous or pulmonary disorders, long-term salicylate therapy, or steroid therapy
- IV in immunocompromised children and adults with viral-mediated complications
- Not recommended for postexposure prophylaxis

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Special Varicella Exposure Situations

Hospital Personnel

Healthcare workers who do not have evidence of varicella immunity and have significant exposure to varicella should be furloughed from day 10 after first exposure to day 21 after last exposure. If workers develop chickenpox, varicella lesions must be crusted before they return to direct patient contact. Receipt of VZIG can prolong the incubation period by one week; the period of furlough should be lengthened to 28 days after last exposure if VZIG is administered.

Newborns

Newborn whose mothers experience rash onset 5 days before to 48 hours after delivery should receive VZIG. Since about 50% of infants who receive VZIG will develop varicella, if these infants remain hospitalized beyond age 10 days, they should be kept in strict isolation for the entire incubation period (until day 28 or longer).

Antiviral Therapy

Several antiviral drugs are active against varicella zoster virus, including acyclovir, valacyclovir, famciclovir, and foscarnet. Valacyclovir and famciclovir are approved for use only in adults. Clinical studies indicate that these drugs may be beneficial if given within 24 hours of onset of rash; they have resulted in a reduction in the number of days new lesions appeared, in the duration of fever, and in the severity of cutaneous and systemic signs and symptoms. Antiviral drugs have not been shown to decrease transmission of varicella, reduce the duration of absence from school, or reduce complications.

The decision to use antiviral therapy, and the duration and route of therapy should be determined by specific host factors, the extent of infection, and the initial response to therapy. ACIP has not made recommendations regarding the use of antiviral therapy for varicella. The American Academy of Pediatrics does not recommend routine antiviral therapy for otherwise healthy infants or children with varicella. Oral acyclovir can be considered for otherwise healthy adolescents and adults or persons with secondary cases in the household because of the increased risk of severe illness in these groups. Antiviral therapy may also be considered for persons with a chronic cutaneous or pulmonary disorders, persons receiving long-term salicylate therapy, and children receiving short, intermittent or aerosolized courses of corticosteroids. If the child is immunocompromised, intravenous administration is indicated. Corticosteroids should be discontinued, if possible, after exposure. Antiviral drugs are not recommended for routine postexposure prophylaxis.

Oral acyclovir is not routinely recommended for pregnant adolescents or adults with uncomplicated varicella because the risks and benefits to the fetus and mother are not known. However, some experts recommend oral acyclovir for pregnant women with varicella, particularly during the second and third trimesters.

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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.

Hepatitis A

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

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 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), 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

Fulminant hepatitis A causes about 100 deaths per year in the United States. The case-fatality rate among persons of all ages with reported cases is approximately 0.3% but can 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 anti-HAV IgM antibody. Acute HAV infection is confirmed during the acute or early convalescent phase of infection by the presence of **anti-HAV IgM** antibody in serum. IgM generally becomes detectable 5–10 days before the onset of symptoms and can persist for up to 6 months.

Anti-HAV IgG antibody 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 anti-HAV IgG and anti-HAV IgM. Persons who are total anti-HAV

positive and anti-HAV IgM 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 Division of Viral Hepatitis, CDC.

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.

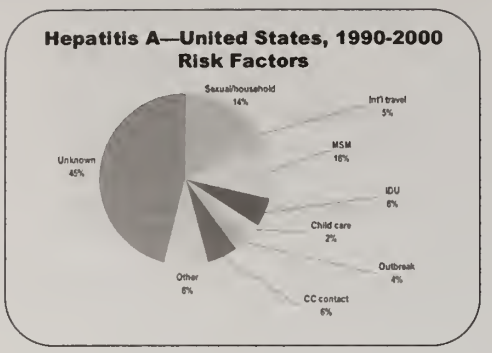
Temporal Pattern

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.

Hepatitis A



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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 person 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 workers 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 record low annual total of 5,970 cases was reported in 2004. After adjusting for underreporting, 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. The wider use of vaccine is probably contributing to this marked decrease in hepatitis A rates in the United States.

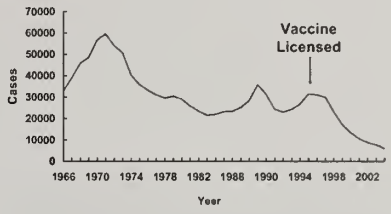
Historically, children 2–18 years of age have had the highest rates of hepatitis A (15–20 cases per 100,000 population in the early to mid 1990s). Since 2002, rates among children have declined and the incidence of hepatitis A is now similar in all age groups.

Based on testing from phase 1 of the Third National Health and Nutrition Examination Survey (NHANES III) conducted during 1988–1994, 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 6–11-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.

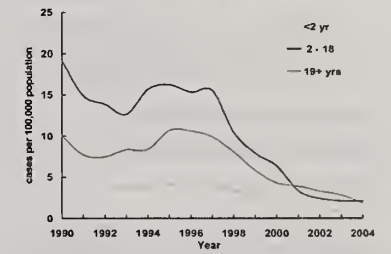
Prior to 2000, the incidence of reported hepatitis A was substantially higher in the western United States than in other parts of the country. From 1987 to 1997, 11 mostly western states (Arizona, Alaska, Oregon, New Mexico, Utah, Washington, Oklahoma, South Dakota, Idaho, Nevada, California) accounted 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 5–10 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

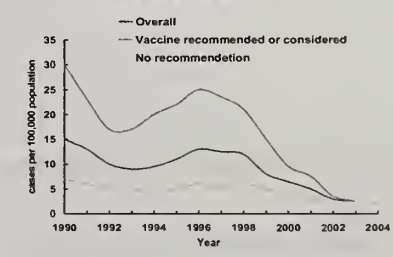
Hepatitis A—United States, 1966-2004



Hepatitis A Incidence By Age Group, 1990-2004



Hepatitis A Incidence By Vaccination Recommendation Status 1990-2004



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%–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 anti-HAV IgM.

Hepatitis A Vaccine

Characteristics

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. Both vaccines were originally licensed for children age 2 years and older. Based on the results of testing among younger children, the Food and Drug Administration approved a reduction to 12 months of age for both vaccines in 2005.

Hepatitis A Vaccines

- Inactivated whole virus
- HAVRIX (GlaxoSmithKline)
- VAQTA (Merck)
- Pediatric and adult formulations
- Licensed for persons >12 months of age

Immunogenicity and Vaccine Efficacy

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.

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 effective in preventing clinical hepatitis A. The efficacy of HAVRIX in protecting against clinical hepatitis A was 94% among 40,000 Thai children 1–16 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 2–16 years of age who received one dose while living in a community with a high HAV disease rate.

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%

Data concerning the long-term persistence of antibody and immune memory are limited because the current vaccines have been available only since 1995–1996. 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.

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

*endorsed by ACIP October 2005; unpublished as of January 2006

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 1987–1997 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 1987–1997 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.

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

*endorsed by ACIP October 2005; unpublished as of January 2006

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 12–23 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. 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 1–18 years of age should receive a single primary dose of the pediatric formulation followed by a booster dose 6–12 months later. Adults 19 years of age and older receive one dose of the adult formulation followed by a booster 6–12 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 (U)	Volume	No. Doses	Schedule*
Children and Adolescents	2-18 years	720	0.5 mL	2	0, 6-12
Adults	>18 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 1–18 years of age should receive one dose of pediatric formulation (25 U per dose) with a booster dose 6–12 months later. Adults 19 years of age and older should receive one dose of adult formulation (50 U per dose) with a booster dose 6–12 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	2-18 years	25	0.5 mL	2	0, 6-18
Adults	>18 years	50	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.

Hepatitis A Vaccines

Adult
- 1 dose
- booster dose 6-18 months after first dose

Children and Adolescent
- 1 dose
- booster dose 6-18 months after first 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.

Studies among adults do not indicate a decrease in immunogenicity or an increase in adverse events when hepatitis A vaccine is administered at the same time as other vaccines. Similar studies among infants are in progress.

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 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. 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 may be used to complete a series begun with Twinrix and vice versa. A person 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.

Twinrix

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

Hepatitis A

Hepatitis A Vaccine Recommendations

- Travelers to high- or intermediate-risk countries
- Protected by 4 weeks after dose
- Give concurrent IG for travel in <4 weeks

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

Hepatitis A Vaccine Recommendations

- Healthcare workers: 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

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. Vaccinated persons can be assumed to be protected by 4 weeks after receiving the first dose, although the second dose 6 to 12 months later is necessary for long-term protection.

Available data suggest that 40%–45% of vaccinated persons might lack neutralizing antibody at 14 days after receiving the first dose. No data are currently available regarding the risk of hepatitis A among persons vaccinated 2–4 weeks before departure. Because protection might not be complete until 4 weeks after vaccination, persons traveling to a high-risk area less than 4 weeks after receiving the initial dose should also be administered immune globulin (0.02 mL/kg) at a different anatomic injection site. Hepatitis A vaccine is not approved for children younger than 1 year of age. Children younger than 1 year of age should receive immune globulin (0.02–0.06 mL/kg, depending on length of stay) prior to travel to high-risk areas.

Other groups which 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 workers, 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 of hepatitis A infection. **ACIP does not recommend routine hepatitis A vaccination for food service workers,** but vaccination may be considered based on local epidemiology.

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 populations. 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.

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.

Hepatitis A Serologic Testing

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

Postvaccination
- not indicated

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.

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.

Hepatitis A Vaccine Adverse Reactions

- Pain at injection site
- Systemic reactions not common
- No serious adverse reactions reported

Contraindications and Precautions to Vaccination

Hepatitis A vaccine should not be administered to persons with a history of a **severe allergic reaction 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

Hepatitis A Vaccine Contraindications and Precautions

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

with moderate or severe acute illnesses should be deferred until the person's condition has improved.

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.

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 Management with Immune Globulin

Standard immune globulin (IG; formerly called gamma globulin) is a concentrated solution of antibodies prepared from pooled human plasma. In the United States, only plasma that has tested negative for hepatitis B surface antigen, antibody to hepatitis C virus, and antibody to human immunodeficiency virus is used to manufacture IG.

Severe adverse reactions from IG are rare. Anaphylaxis has been reported after repeated administration to persons who have known IgA deficiency; thus, IG should not be administered to these persons. Pregnancy or lactation is not a contraindication to IG use.

When administered intramuscularly before exposure to HAV, or within 2 weeks after exposure, IG is more than 85% effective in preventing hepatitis A. Later administration of IG often only attenuates the clinical expression of HAV infection.

An appropriately large muscle mass (e.g., the deltoid or gluteal muscle) should be used as the site of the injection. A single intramuscular dose of 0.02 mL/kg of IG confers protection for less than 3 months; 0.06 mL/kg protects for 5 months. IG should be given to exposed persons who have not previously received hepatitis A vaccine as soon as possible, but not more than 2 weeks after the exposure.

Recipients may include persons who had close contact (household or sexual) with a person with hepatitis A; staff

and attendees at child care centers where a hepatitis A case has been recognized; and persons in certain common-source exposure situations (e.g., patrons of a food establishment with an HAV-infected food handler, if the risk of transmission is determined to be high). Persons who have received one dose of hepatitis A vaccine at least 1 month before an HAV exposure do not need IG.

IG can interfere with the response to live injected vaccines (e.g., measles, mumps, rubella, and varicella vaccines). Administration of live vaccines should be delayed for at least 3 months after administration of IG (see Chapter 2, General Recommendations on Immunization.) Conversely, unless the benefits of IG prophylaxis exceed the benefits of vaccination, IG should not be administered for at least 2 weeks after measles-, mumps-, and rubella-containing vaccines, and for 3 weeks after vaccination with varicella vaccine. If IG is given during this period, the person should be revaccinated with the live vaccine, but not sooner than 3 months after administration of IG.

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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 1883. 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 at least a month at room temperature.

Hepatitis B Virus

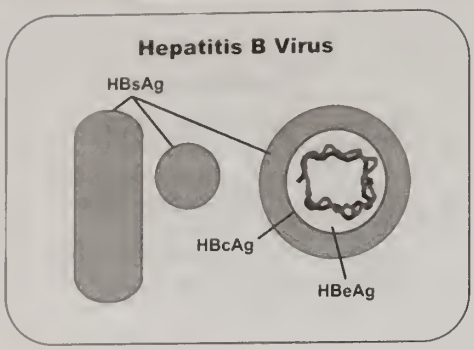
- Hepadnaviridae family (DNA)
- Numerous antigenic components
- Humans are only known host
- May retain infectivity for at least 1 month at room temperature

HBV is the most common known cause of chronic viremia, with more than 200 million chronically infected persons estimated worldwide. HBV infection is an established cause of acute and chronic hepatitis and cirrhosis. It is the cause of up to 80% of hepatocellular carcinomas, and is second only to tobacco among known human carcinogens. More than 250,000 persons die worldwide each year of hepatitis B-associated acute and chronic liver disease.

Hepatitis B Virus Infection

- >200 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.

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

Clinical Features

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 10 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 1 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.

Chronic HBV Infection

Approximately 10% 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%.

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.

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

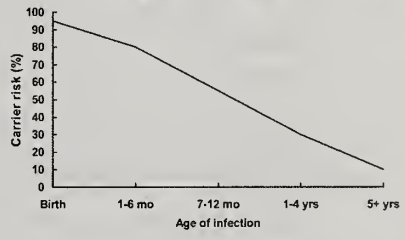
Hepatitis B Complications

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

Chronic Hepatitis B Virus Infection

- Chronic viremia
- Responsible for most mortality
- Overall risk 10%
- Higher risk with early infection

Risk of Chronic HBV Carriage by Age of Infection



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 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.

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.

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 15% 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

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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

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

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.

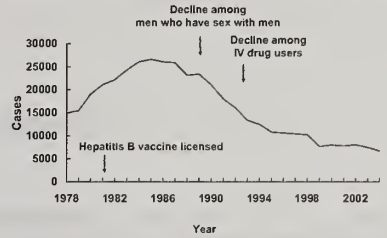
The incidence of reported hepatitis B peaked in the mid-1980s, with about 26,000 cases reported each year. Reported cases have declined since that time, and fell below 10,000 cases for the first time in 1996. The decline in cases during the 1980s and early 1990s is generally attributed to reduction of 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 6,741 cases of hepatitis B were reported in 2004.

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—United States, 1978-2004

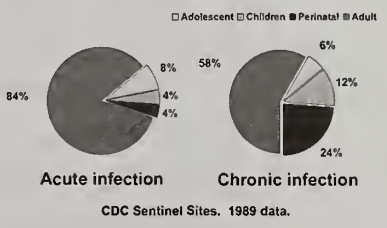


HBV Disease Burden in the United States*

New infections	78,000/yr
Current carriers	>1 million
New carriers	>5,000/yr
Death	5,000/yr

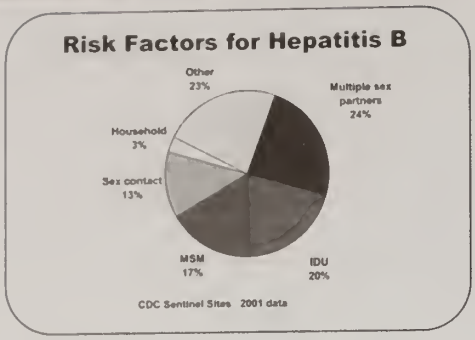
*2001 estimates

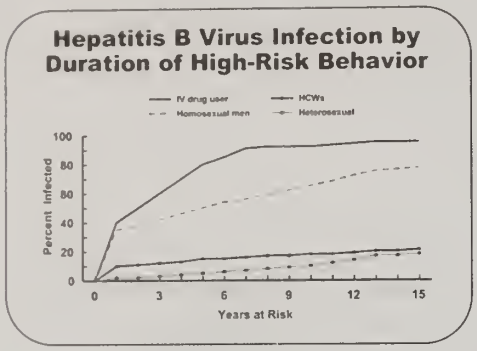
Age of Infection of Acute and Chronic Hepatitis B Virus Infection



CDC Sentinel Sites. 1989 data.

Hepatitis B





The most common risk factor for HBV infection in the United States is sexual contact, either heterosexual (37%), or among men who have sex with men (17%). Injection-drug use accounts for 20% of cases, and 3% of cases occur by household contact with a chronically infected person. In the early 1990s, healthcare workers accounted for approximately 1% of HBV infections. With widespread use of hepatitis B vaccine, HBV infection among healthcare workers is now very uncommon.

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 institutions for the developmentally disabled.	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 workers – frequent blood contact.	1-2	15-30
	Staff of institutions for the mentally retarded.	1	10-25
	Heterosexuals with multiple partners.	0.5	5-20
Low-Risk	Healthcare workers – 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.

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 human carriers. 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, and was the first licensed vaccine in the United States produced by recombinant DNA technology. 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	>15 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 11–15 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 (11–19 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, 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	0	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 age 0, 1, and 6 months.
‡ Two 1.0 mL doses administered at one site, on a 4-dose schedule at age 0, 1, 2, and 6 months.
** Not applicable.

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.

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

Available data show that vaccine-induced antibody levels decline with time. Nevertheless, immune memory remains intact for more than 15 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.

Hepatitis B Vaccine

Routine booster doses are NOT routinely recommended for any group

For adults and children with normal immune status, **booster doses of vaccine are not recommended, nor is routine serologic testing to assess immune status of vaccinees indicated.** 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, 1-2, and 6–18 months. Infants whose mothers are HBsAg positive or whose HBsAg status is unknown should receive the third dose by 6 months of age.

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

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) beginning at or shortly after birth. 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 <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 12–15 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 9, *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

- DTaP – Hep B – IPV combination
- Approved for 3 doses at 2, 4 and 6 months
- Not approved for booster doses
- Licensed for children 6 weeks to 7 years of age

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.

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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 unknown

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.

Hepatitis B Vaccine Adolescent Vaccination

- Routine vaccination recommended through age 18 years
- Integrate into routine adolescent immunization visit
- Flexible schedules

Adolescents (11–19 Years of Age)

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 11–12 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).

Adolescents 11–19 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 4–6 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 11–15 years of age. This alternative schedule is for two 10-mcg doses of Recombivax HB separated by 4–6 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 11–15 years of age, and for Merck's hepatitis B vaccine. The 2-dose schedule should be completed by age 16 years.

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 4–6 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 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 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

Adult Hepatitis B Vaccine Candidates

- Men who have sex with men
- Heterosexual with multiple partners
- Persons diagnosed with an STD
- Prostitutes
- Injection drug users
- Inmates of long-term correctional facilities
- Persons receiving hemodialysis
- Healthcare workers

Adults who are at increased risk of HBV infection from sexual transmission include **men who have sex with other men, heterosexuals with multiple sex partners, persons diagnosed with a recently acquired sexually transmitted disease, and prostitutes.**

Injection-drug users who share needles are at very high risk for HBV infection. All injection-drug users who are susceptible to HBV should be vaccinated as soon as possible after their drug use begins.

Inmates of long-term correctional facilities are at increased risk of HBV infection because of injection-drug use, homosexual activity, or other factors. The prison setting provides an access point for vaccination of inmates with histories of high-risk behavior.

Persons undergoing hemodialysis are at increased risk of HBV infection because of contact with large amounts of blood. Although the hepatitis B vaccine is less effective in these patients, it is recommended for all susceptible hemodialysis patients.

The risk of **healthcare workers** contracting HBV infection depends on how often they are exposed to blood or blood products through percutaneous and permucosal exposures. Any healthcare or public safety worker may be at risk for HBV exposure, depending on the tasks performed. If those tasks involve contact with blood or blood-contaminated body fluids, such workers should be vaccinated. Risk is often highest during training periods. Therefore, it is recommended that vaccination be completed during training in schools of medicine, dentistry, nursing, laboratory technology, and other allied health professions.

Twinrix

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

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. 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 14, Hepatitis A, for details.

Other Groups Who May Be Candidates for Hepatitis B Vaccine

The special behavioral and medical problems encountered in **institutions for the developmentally disabled** make this a high-risk setting, and clients and staff should be vaccinated. The risk of HBV infection in these institutions is related to contact with blood and also with bites and contact with skin lesions and other body fluids that contain HBV. Clients and staff of group and foster homes where a chronically infected person is known to be present should also be vaccinated.

Other Hepatitis B Vaccine Candidates

- Staff of institutions for developmentally disabled
- Alaska Natives, Pacific Islanders
- Immigrants/refugees*
- Adoptees, orphans, unaccompanied minors*
- Household members and sex partners of HBV carriers
- Extended travel to areas of high endemicity
- Recipients of certain blood products

*from countries of high or intermediate HBV endemnicity

In certain U.S. populations, such as **Alaska Natives, Pacific Islanders, and immigrants and refugees from HBV-endemic areas**, HBV infection is highly endemic and transmission occurs primarily during childhood. In such groups, vaccination of all infants is particularly important. Immigrants and refugees from areas with highly endemic HBV disease should be screened for HBV upon resettlement in the United States. If a chronically infected person (carrier) is identified, all susceptible household members should be vaccinated. Even if no carriers are found, vaccination is recommended for susceptible children younger than 7 years of age because of the high rate of interfamilial spread of HBV.

Adoptees, orphans, and unaccompanied minors from countries of high or intermediate HBV endemicity should be screened for HBsAg, and, if positive, their household members should be vaccinated.

Household members and sex partners of HBV carriers should be tested and, if susceptible (i.e., neither anti-HBs positive [immune] or HBsAg positive [acutely or chronically infected]), should be vaccinated.

Adults and children who plan to travel to areas outside the United States that have high rates of HBV infection should be vaccinated if they plan to stay in these areas for more than 6 months and have close contact with the local population. Persons traveling for shorter durations who may have sexual contact with local persons in areas where HBV infection is common should also be vaccinated. Persons traveling abroad who will perform medical procedures in areas where HBV infection is common are at very high risk.

Recipients of certain blood products, such as persons with hemophilia, are at high risk of infection. Vaccination should be initiated at the time their specific clotting disorder is identified.

Persons who have casual contact with chronically infected persons at schools and offices are at low risk of HBV infection from such contact, and vaccine is not recommended for this group. Unless special circumstances exist, such as behavior problems (biting or scratching) or medical conditions (severe skin disease) that might facilitate transmission, vaccination of contacts of carriers in child care centers is not indicated. However, routine vaccination of all persons 18 years of age and younger is recommended.

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. Screening is usually cost-effective, and should be considered, in 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, Alaska natives, Pacific Islanders, children of immigrants from endemic-disease countries, and family members of HBsAg-positive 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.

Prevaccination Serologic Testing

- Not indicated before routine vaccination of infants or children
- May be considered when vaccinating adolescents in groups with high rates of HBV infection
  - –Alaska Natives
  - –Pacific Islanders
  - –children of immigrants from endemic countries
  - –family members of HBV carriers

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Postvaccination Serologic Testing

Testing for immunity following vaccination is not recommended routinely but should be considered for persons whose subsequent management depends on knowing their immune status, such as dialysis patients and staff, and persons in whom a suboptimal response may be anticipated, such as those who have received vaccine in the buttock. Testing is also recommended for sex partners of HBsAg-positive persons. When necessary, postvaccination testing should be performed 1–2 months after completion of the vaccine series.

All infants born to HBsAg-positive women should be tested 3–12 months after their final (third or fourth) dose of hepatitis B vaccine (i.e., at 9–18 months of age). If HBsAg is not present and anti-HBs antibody is present, children can be considered to be protected.

Postvaccination Serologic Testing

- Not routinely recommended following vaccination of infants, children, adolescents, or most adults
- Recommended for:
  - –hemodialysis patients
  - –infants born to HBsAg+ women
  - –sex partners of HBsAg+ person
  - –immunodeficient persons
  - –certain healthcare workers

In 1997, ACIP and the Hospital Infection Control Practices Advisory Committee published comprehensive recommendations for the immunization of healthcare workers. One of the recommendations was that **healthcare workers 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 vaccination.** However, a catch-up program of serologic testing for healthcare providers vaccinated prior to December 1997 was not recommended. These persons should be tested as necessary if they have a significant exposure to HBV (see postexposure prophylaxis section below).

Postvaccination Serologic Testing

Healthcare workers who have contact with patients or blood should be tested for antibody after vaccination

Routine postvaccination testing is **not** recommended for persons at low risk of exposure, such as public safety workers and healthcare workers 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.

Management of Nonresponse to Hepatitis B Vaccine

- Complete a second series of three doses
- Should be given on the usual schedule of 0, 1 and 6 months
- Retest 1-2 months after completing the second series

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 workers and others for whom postvaccination serologic testing is recommended should be retested 1–2 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

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

probable parenteral exposure to HBsAg-positive blood (see postexposure prophylaxis table on page 228).

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, 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) 9–15 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 1–2 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 4–6 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, below).

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 1–2 months and 6 months, respectively, after the first. Testing for HBsAg and anti-HBs is recommended at 9–18 months of age (3–12 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.

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

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 1–2 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 9–18 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 1–2 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 (see http://www.cdc.gov/nip/vfc/acip_recs/1003hepb.pdf). **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.

Recommended Postexposure Prophylaxis for 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

Susceptible Sex Partners of Persons with Acute or Chronic HBV Infection

For susceptible sex partners of persons with acute HBV infection, a single dose of HBIG (0.06 mL/kg) given within 14 days of the last sexual contact is recommended. If the last sexual contact was more than14 days previously, hepatitis B vaccination should be initiated, although the amount of protection afforded by postexposure prophylaxis given this late is not known. For sex partners of persons with chronic HBV infection, postexposure prophylaxis with hepatitis B vaccine alone is recommended. HBIG is not recommended in this situation. Postvaccination anti-HBs antibody testing should be considered for sex partners of persons with chronic HBV infection.

Household Contacts of Persons with Acute HBV Infection

Infants whose mother or primary caregiver has acute HBV infection are at increased risk of developing chronic HBV infection because of close contact. An unvaccinated infant whose mother or primary caregiver has acute HBV infection should receive HBIG (0.5 mL) along with the first dose of the hepatitis B vaccine series. HBIG is not needed for infants who have received two doses of vaccine or who are scheduled to receive the second dose of vaccine. The second vaccine dose should be given and/or vaccination should be completed on schedule. Household contacts of persons with acute HBV infection who have had a blood exposure to the infected person (e.g., sharing a toothbrush or razor) should receive HBIG and begin the vaccine series. Routine hepatitis B vaccination should be considered for nonsexual household contacts who do not have a blood exposure to the infected person, especially for children and adolescents.

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.

Hepatitis B Vaccine
Contraindications and Precautions

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

Contraindications and Precautions to Vaccination

A severe allergic reaction 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.

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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15

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.

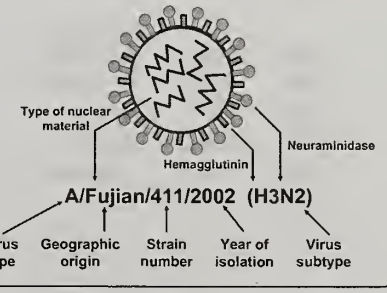
Influenza Virus

- 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

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

and are selected as the predominant virus to the extent that 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.

During the past 100 years, 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 generally 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.

"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

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

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.

Influenza Complications

- Pneumonia
  - —secondary bacterial
  - —primary influenza viral
- Reye syndrome
- Myocarditis
- Death 0.5-1 per 1,000 cases

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 recent 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.

Impact of Influenza

- ~36,000 excess deaths per year
- >90% of deaths among persons ≥65 years of age
- Higher mortality during seasons when influenza type A (H3N2) viruses predominate

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

Impact of Influenza

- Highest rates of complications and hospitalization among young children and person ≥65 years
- Average of >200,000 influenza-related excess hospitalizations
- 57% of hospitalizations among persons <65 years of age
- Greater number of hospitalizations during type A (H3N2) epidemics

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 12 months of age and younger are comparable to rates for persons 65 and older. To reduce the risk of hospitalization from complications of influenza, the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Pediatrics recommend routine annual influenza vaccination of children 6–23 months of age.

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/

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

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.

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

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 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/labdiagnosis.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 1976–2005, peak influenza activity in the United States occurred most frequently in January (21% of seasons) and February (45% of seasons). However, peak influenza activity occurred in March, April, or May in 16% 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.

Influenza Epidemiology

• Reservoir	Human, animals (type A only)
• Transmission	Respiratory Probably airborne
• Temporal pattern	Peak December – March In temperate climate May occur earlier or later
• Communicability	1 day before to 5 days after onset (adults)

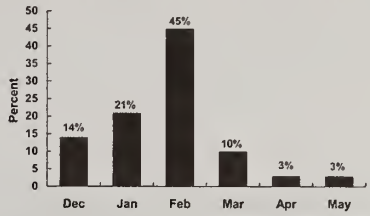
Secular Trends in the United States

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.

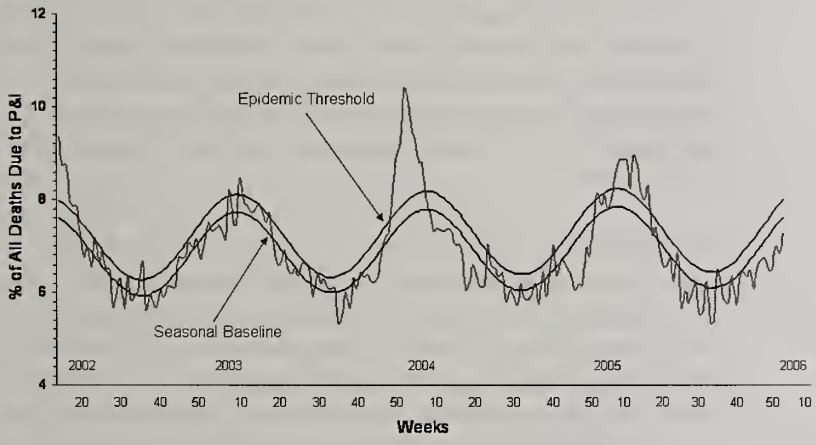
The impact of influenza in the United States is quantified by measuring pneumonia and influenza (P and I) deaths. Death certificate data are collected from 122 U.S. cities with populations of more than 100,000 (total of approximately 70,000,000). P and I deaths include all deaths for which pneumonia 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.

Month of Peak Influenza Activity
United States, 1976-2005



Pneumonia and Influenza Mortality
for 122 U.S. Cities
Week Ending 01/07/2006



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 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.

Influenza Vaccines

- **Inactivated subunit (TIV)**
  - **—intramuscular**
  - **—trivalent**
- **Live attenuated vaccine (LAIV)**
  - **—intranasal**
  - **—trivalent**

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 2005–2006 influenza season three 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 was the only TIV approved for use among children younger than 48 months during the 2005–2006 season. Fluvirin (Chiron) was available in multidose vials and reduced-thimerosal ("preservative free") single-dose syringes. 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. These manufacturers will probably supply TIV to the U.S. market in 2006.

Live attenuated influenza vaccine (LAIV) was approved for use in the United States in 2003. LAIV is administered by the intranasal route and contains the same three influenza viruses as TIV. The live attenuated influenza viruses in LAIV are **temperature-sensitive**, so they do not replicate effectively at core body temperature (100.4°–102.2°F [38°–39° C]). The viruses are also **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.

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.

Vaccinated children can shed vaccine viruses in nasopharyngeal secretions for up to 3 weeks. In one study in a child care setting, 80% of vaccinated children 8–36 months of age shed at least one virus strain for an average of 7.6 days. In this study, one instance of transmission of vaccine virus to a contact was 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. Priming by prior infection with a closely related strain or prior vaccination enhances immunologic response after vaccination.

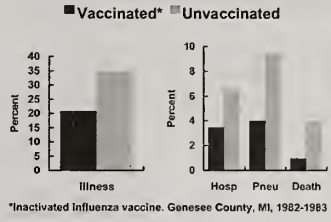
Inactivated Influenza Vaccine Efficacy

- 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

Influenza vaccine efficacy varies by the similarity of the vaccine strain(s) to the circulating strain 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 frail 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. There is no evidence 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

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 workers
- Vaccination of all other groups should begin in November
- Continue vaccinating through December and later, as long as vaccine is available

patient visits. Organized campaigns for persons in high-risk groups who are routinely accessible are best undertaken in October and November. The ACIP recommends that high-risk populations, healthcare workers, and children younger than 9 years of age being vaccinated for the first time should begin vaccinations in October. All other groups should begin vaccinations in November. 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.

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 influenza vaccine during a previous 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 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 6–23 months 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 to 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

Inactivated Influenza Vaccine Recommendations

- All persons 50 years of age or older
- Children 6-23 months of age
- Residents of long-term care facilities
- Pregnant women
- Persons 6 months to 18 years receiving chronic aspirin therapy
- Persons ≥6 months of age 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

- 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 recent 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.

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.**

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

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.

Studies have examined the effect of inactivated influenza vaccine on replication of HIV. Some studies have demonstrated a transient increase in viral titer in the blood of vaccinated persons infected with HIV. This phenomenon has also been reported after other vaccines, such as tetanus toxoid and pneumococcal polysaccharide vaccines. Not all studies produced these findings; other investigators using similar methods have not documented increased HIV titers after influenza vaccination. Although HIV titers may increase transiently, 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.**

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

Influenza Vaccine Recommendations

- Healthcare providers, including home care*
- Employees of long-term care facilities
- Household contacts of high-risk persons

*LAIV should not be administered to healthcare workers who have contact with severely immunosuppressed persons who require hospitalization and care in a protective environment

Influenza Vaccine Recommendations*

- Providers of essential community services
- Students
- Persons traveling outside the U.S.
- Anyone who wishes to reduce the likelihood of becoming ill from influenza

*these groups may receive TIV, and some may be eligible for LAIV

Influenza Vaccination of Children

- Children <24 months at increased risk of hospitalization
- Inactivated influenza vaccination of healthy children 6-23 months is recommended
- Vaccination of household contacts and other caregivers of children <24 months of age is encouraged

Live Attenuated Influenza Indications

- Healthy* persons 5-49 years of age
  - —close contacts of persons at high risk for complications of influenza (except immunosuppressed)
  - —persons who wish to reduce their own risk of influenza

*Persons who do not have medical conditions that increase their risk for complications of influenza

Persons who have contact with high-risk persons should receive TIV. These include **healthcare workers, 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 workers 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. The most current available vaccine should be used. Any person who wishes to lessen his/her chance of acquiring influenza infection may be vaccinated. These groups may receive TIV, and some may be eligible for LAIV (see table).

Beginning in 2004, the ACIP recommended that healthy children aged 6–23 months be vaccinated because of the increased risk of influenza-related hospitalization in this age group. Household contacts and other caregivers of children younger than 24 months of age are also encouraged to receive annual influenza vaccination.

LAIV

The optimum timing of LAIV has not been determined. 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 9–49 years of age. Children 5–8 years of age receiving influenza vaccine for the first time should receive two doses administered 6–10 weeks apart.

Live Attenuated Influenza Vaccine Dosage, by Age Group – United States

Age Group	Number of Doses	Route
5-8 years, no previous influenza vaccine	2 (separated by 6-10 weeks)	Intranasal
5-8 years, previous influenza vaccine*	1	Intranasal
9-49 years	1	Intranasal

*LAIV or inactivated vaccine

Live attenuated influenza vaccine is approved by the Food and Drug Administration only for use among healthy persons 5–49 years of age. Persons in this group, including most persons in close contact with high-risk groups and those wishing to reduce their risk of influenza, now have the option of choosing either inactivated vaccine or LAIV.

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., 5–49 years of age and healthy). Persons in close contact with severely immunosuppressed persons who are hospitalized and receiving care in a protected environment should not receive LAIV.

The manufacturer's package insert recommends that LAIV not be administered concurrently with other vaccines, because it is not known whether concurrent administration of LAIV with other vaccines affects the safety or efficacy of either LAIV or the simultaneously administered vaccine. In the absence of specific data indicating interference, ACIP recommends that providers follow the guidelines for simultaneous administration published in the General Recommendations on Immunization. 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

Inactivated Influenza Vaccine Adverse Reactions

Local reactions	15%-20%
Fever, malaise	not common
Allergic reactions	rare
Neurological reactions	very rare

Adverse Reactions Following Vaccination

TIV

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.

Although influenza vaccination can inhibit the clearance of warfarin and theophylline, studies have failed to show any adverse clinical effects attributable to these drugs among patients receiving influenza vaccine.

LAIV

The safety of the approved LAIV has been assessed in 20 prelicensure clinical trials. More than 6,000 study participants were in the approved age range of 5–49 years. Among healthy children, there were no significant differences between vaccine and placebo recipients in the proportion with upper respiratory symptoms such as runny nose and nasal congestion, fever, or other systemic symptoms. These symptoms were reported in 10%–40% of both vaccine and placebo recipients. Data from an unpublished study suggested **a significantly increased risk of asthma or reactive airways disease among children 12–59 months of age** who received LAIV. Because of this, LAIV is not approved for use in

Live Attenuated Influenza Vaccine Adverse Reactions

- Children
  - —no significant increase in URI symptoms, fever, or other systemic symptoms
  - —significantly increased risk of asthma or reactive airways disease in children 12-59 months of age
- Adults
  - —significantly increased rate of cough, runny nose, nasal congestion, sore throat, and chills reported among vaccine recipients
  - —no increase in the occurrence of fever
- No serious adverse reactions identified

children younger than 60 months of age, and it should not be used in persons with asthma, reactive airways disease, or other chronic pulmonary diseases.

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.

Contraindications and Precautions to Vaccination

TIV

Persons with a **severe allergic reaction** to a prior dose of inactivated influenza vaccine, or to a vaccine component (e.g., eggs) 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.

LAIV

Persons who should **not** receive LAIV include children younger than 5 years of age; persons 50 years of age and older; persons with chronic medical conditions, including asthma, reactive airways disease or other chronic pulmonary or cardiovascular conditions, 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.

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

Live Attenuated Influenza Vaccine Contraindications and Precautions

- Children <5 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

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.

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 must be stored at 5°F (-15°C) or colder. LAIV may now be stored in a frost-free freezer that has a separate door (i.e., not in a dormitory-style refrigerator-freezer unit). LAIV can be thawed in a refrigerator and stored at 35°–46°F (2°–8°C) for up to 60 hours before use. It should not be refrozen after thawing.

LAIV is intended for intranasal administration only and should never be administered by injection. LAIV must be thawed before administration. If the vaccine is not thawed in a refrigerator, this can be accomplished by holding an

LAIV Storage and Handling

- Must be stored at ≤ 5°F (-15°C)
- May be stored in a frost-free freezer with a separate door
- May be thawed in a refrigerator and stored at 35°-46°F (2°-8°C) for up to 60 hours before use
- Should not be refrozen after thawing

individual sprayer in the palm of the hand until thawed and then administering the vaccine immediately. LAIV is supplied in a prefilled single-use sprayer containing 0.5 mL of vaccine. Approximately 0.25 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 chronic care facilities) and to reduce epidemic-related pneumonia and influenza-related deaths among persons 65 years of age and older. In 2003, 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.

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),

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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

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. Amantadine and rimantadine are effective against type A influenza only and are approved by the Food and Drug Administration for both influenza A prophylaxis and treatment of persons 1 year of age and older.

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. Oseltamivir is approved for prophylaxis of influenza infection among persons 13 years of age and older. Zanamivir is not approved for prophylaxis.

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 www.cdc.gov/flu.

Influenza Antiviral Agents*

- **Amantadine and rimantadine**
  - —effective against influenza A only
  - —approved for prophylaxis and treatment
- **Zanamivir and oseltamivir**
  - —neuraminidase inhibitors
  - —effective against influenza A and B
  - —oseltamivir approved for prophylaxis

*see influenza ACIP statement or CDC influenza website for details

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 preventive action (e.g., chemoprophylaxis of unvaccinated high-risk patients).

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

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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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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.

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

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.

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.

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

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.

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

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 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.

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

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

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.

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

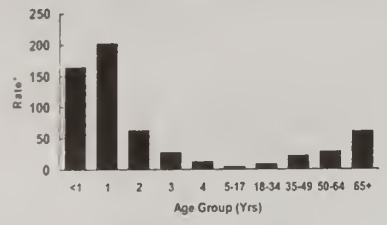
Estimates of the incidence of pneumococcal disease have been made from a variety of population-based studies. More than 40,000 cases and more than 5,500 deaths from invasive pneumococcal disease (bacteremia and meningitis) are estimated to have occurred in the United States in 2002. More than half of these cases occurred in adults who had an

Pneumococcal Disease Epidemiology

• Reservoir	Human carriers
• Transmission	Respiratory Autoinoculation
• Temporal pattern	Winter and early spring
• Communicability	Unknown Probably as long as organism in respiratory secretions

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.

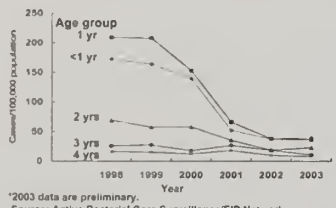
Invasive Pneumococcal Disease Incidence by Age Group—1998



*Rate per 100,000 population
Source: Active Bacterial Core surveillance/EIP Network

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.

Invasive Pneumococcal Disease by Age and Year—Children <5 Years, 1998-2003*



*2003 data are preliminary.
Source: Active Bacterial Core Surveillance/EIP Network

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 2003 indicate that rates of invasive pneumococcal disease have declined 70%–80% among children younger than 2 years of age, compared with 1998–1999 (prior to licensure of the vaccine). Rates of invasive disease have also declined among older age groups, although the decline is less than among young children. The decline among older age groups may indicate a reduction in transmission from vaccinated children to their household and other close contacts.

Pneumococcal Disease Outbreaks

- Outbreaks not common
- Generally occur in crowded environments (jails, nursing homes)
- Persons with invasive disease often have underlying illness
- May have high fatality rate

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

Pneumococcal Vaccines

1977	14-valent polysaccharide vaccine licensed
1983	23-valent polysaccharide vaccine licensed (PPV23)
2000	7-valent polysaccharide conjugate vaccine licensed (PCV7)

(PPV23) was licensed and replaced the 14-valent vaccine, which is no longer produced. PPV23 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 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 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

- 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 PPV23 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.

PPV23 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

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

severe disease. PPV23 has not been demonstrated to provide protection against pneumococcal pneumonia. For this reason, providers should avoid referring to PPV23 as "pneumonia vaccine."

Studies comparing patterns of pneumococcal carriage before and after PPV23 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

- 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

Pneumococcal Conjugate Vaccine

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 Recommendations

- Adults ≥65 years of age
- Persons ≥2 years with
  - —chronic illness
  - —anatomic or functional asplenia
  - —immunocompromised (disease, chemotherapy, steroids)
  - —HIV infection
  - —environments or settings with increased risk

Pneumococcal Polysaccharide Vaccine

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, or cerebrospinal fluid leak.

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.

If elective splenectomy is being considered, the vaccine should be given at least 2 weeks before the operation. If vaccination prior to splenectomy 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 PPV23 (see Revaccination below).

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 child needs to complete the series depends on the child's current age. Unvaccinated children aged 7–11 months should receive two doses of vaccine at least 4 weeks apart, followed by a booster dose at age 12–15 months. Unvaccinated children aged 12–23 months should receive two doses of vaccine, at least 8 weeks apart. Previously

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

unvaccinated healthy children aged 24–59 months should receive a single dose of PCV7. Unvaccinated children aged 24–59 months with sickle cell disease, asplenia, HIV infection, chronic illness, 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 PPV23. Children 24–59 months of age who have already received PPV23 and who are at high risk of invasive pneumococcal disease (sickle cell disease, asplenia, HIV infection or other immunocompromising conditions or chronic diseases) could benefit from the immunologic priming induced by PPV23. 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 PPV23. Similarly, children 24–59 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 PPV23. Vaccination with PPV23 should be considered for these high-risk children. PPV23 should be given no sooner than 2 months after the last dose of PCV7. Routine administration of PPV23 to healthy children 24–59 months of age is not recommended.

Revaccination

Pneumococcal Polysaccharide Vaccine

Following vaccination with PPV23, 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 PPV23**

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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

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.

Adverse Reactions Following Vaccination

Pneumococcal Polysaccharide Vaccine

The most common adverse reactions following either pneumococcal polysaccharide or conjugate vaccine are **local reactions**. For PPV23, 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 PPV23 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 PPV23 vaccine. No clinical or immunologic deterioration has been reported in these persons.

Pneumococcal Vaccines Adverse Reactions

• Local reactions	
–polysaccharide	30%-50%
–conjugate	10%-20%
• Fever, myalgia	
–polysaccharide	<1%
–conjugate	15%-24%
• Severe adverse reactions	rare

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.

Pneumococcal Vaccines
Contraindications and Precautions

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

Contraindications and Precautions to Vaccination

For both pneumococcal polysaccharide and conjugate vaccines, a **severe allergic reaction** 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.

The safety of PPV23 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.

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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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.

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)

For instance, serogroup A is a major cause of 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.

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.

Meningococcal Disease Pathogenesis

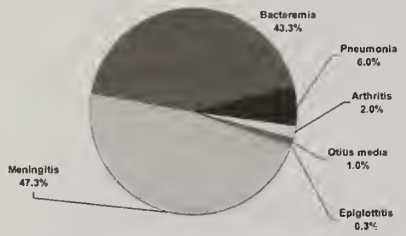
- Organism colonizes nasopharynx
- In some persons organism invades bloodstream and causes infection at distant site
- Antecedent URI may be a contributing factor

Clinical Features

The incubation period of meningococcal disease is 3–4 days, with a range of 2–10 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.

Neisseria meningitidis* Clinical Manifestations



*1992-1996 data

Meningococcal sepsis (bloodstream infection or meningococcemia) occurs without meningitis in 5%–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.

Meningococcal Meningitis

- Most common pathologic presentation
- Result of hematogenous dissemination
- Clinical findings
  - —fever
  - —headache
  - —stiff neck

Less common presentations of meningococcal disease include pneumonia (5%–15% of cases), arthritis (2%), otitis media (1%), and epiglottitis (less than 1%).

The **case-fatality rate** of invasive meningococcal disease is 9%–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.

Meningococcemia

- Bloodstream infection
- May occur with or without meningitis
- Clinical findings
  - —fever
  - —petechial or purpuric rash
  - —hypotension
  - —multiorgan failure

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 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.

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

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.

Meningococcal Disease
Laboratory Diagnosis

- Bacterial culture
- Gram stain
- Non-culture methods
  - —antigen detection in CSF
  - —serology

Meningococcal Disease

Neisseria meningitidis
Medical Management

- Initial empiric antibiotic treatment after appropriate cultures are obtained
- Treatment with penicillin alone recommended after confirmation of *N. meningitidis*

Meningococcal Disease
Epidemiology

• Reservoir	Human
• Transmission	Respiratory droplets
• Temporal pattern	Peaks in late winter and early spring
• Communicability	Generally limited

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.

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

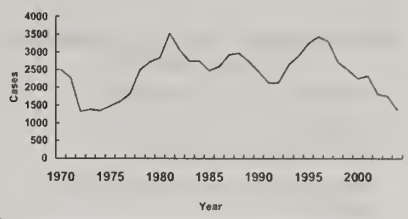
Approximately 2,000 to 3,000 cases of meningococcal disease are reported each year in the United States (0.8–1.3 cases per 100,000 population). In 2004, an estimated 125 deaths due to meningococcal disease occurred in the United States. Infants younger than 12 months of age have the highest rates of 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.

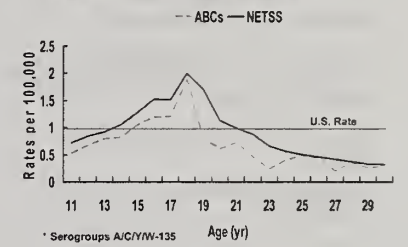
Large outbreaks of serogroup A meningococcal disease occur in the African "meningitis belt," an area that extends from Ethiopia to Senegal. Rates of endemic meningococcal disease in this area are several times higher than in industrialized countries. In addition, outbreaks occur every 8–12 years with attack rates of 500–1000 cases per 100,000 population.

Meningococcal Disease—United States, 1972-2004



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 (MPSV)

- Menomune (sanofi pasteur)
- Quadrivalent polysaccharide vaccine (A, C, Y, W-135)
- Administered by subcutaneous injection
- 10-dose vial contains thimerosal as a preservative

Meningococcal Conjugate Vaccine (MCV)

- 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 Vaccines

Characteristics

Meningococcal Polysaccharide Vaccine (MPSV)

The first meningococcal polysaccharide vaccine (Menomune, sanofi pasteur) was licensed in the United States in 1974. The current quadrivalent A, C, Y, W-135 polysaccharide vaccine 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.

MPSV 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 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 (MCV)

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.

MCV 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 MPSV 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, no 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, measurable levels of antibodies against serogroup A and C polysaccharides decrease 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 MCV was based on studies that compared the serologic response to a single dose 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 MCV as those who received MPSV. 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 MCV, it is believed that this vaccine will have a longer duration of protection than for MPSV. In addition, MCV 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 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, MPSV 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 MPSV 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 MPSV should be limited to persons 2–10 years and older than 55 years of age, or when

MPSV Recommendations

- **Approved for persons ≥2 years of age**
- **Not recommended for routine vaccination of civilians**
- **Should be used only for persons at increased risk of *N. meningiditis* infection who are 2-10 years or >55 years of age, or if MCV is not available**

MCV Recommendations

- Routinely recommended for:
  - —all children at 11-12 years of age
  - —unvaccinated children at entry to high school (age 15 years)
  - —all college freshmen living in a dormitory
  - —other persons 11-55 years of age at increased risk of invasive meningococcal disease

MMWR 2005; 54(RR-7);1-21

Meningococcal Vaccine Recommendations

- Use of MCV is preferred for persons 11-55 years of age for whom meningococcal vaccine is recommended
- MPSV should be used for persons 2-10 years and >55 years
- Use of MPSV is an acceptable alternative for persons 11-55 years of age if MCV is not available

MMWR 2005; 54(RR-7);1-21

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

MMWR 2005; 54(RR-7);1-21

Meningococcal Endemic Areas 2004

MCV is not available. MPSV can be administered at the same visit as other indicated vaccines. All vaccines should be given at separate sites with separate syringes.

Meningococcal Conjugate Vaccine

MCV should be administered to all children at 11–12 years of age as well as to unvaccinated adolescents at high school entry (age 15 years). Other adolescents who wish to decrease their risk for meningococcal disease may also be vaccinated. All college freshmen living in dormitories should also be vaccinated.

MCV if preferred for routine vaccination of adolescents and persons 11–55 years of age who are at increased risk of meningococcal disease. MPSV is an acceptable alternative for persons 11–55 years of age if MCV if 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.**

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). Therefore, 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.

MCV can be administered at the same visit as other indicated vaccines. All vaccines should be given at separate sites with separate syringes.

Both MCV and MPSV 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.

Revaccination

Revaccination may be indicated for persons previously vaccinated with MPSV 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 2–3 years if they remain at high risk. Although the need for revaccination of older children and adults after receiving MPSV 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. MCV is recommended for revaccination of persons 11–55 years of age. However, use of MPSV is acceptable.

The Advisory Committee on Immunization Practices (ACIP) expects that MCV will provide longer protection than MPSV. 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 MCV. At the present time, revaccination after receipt of MCV is not recommended.

Meningococcal Vaccine Recommendations

- Both MCV and MPSV 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-baeed rates should be used rother than age-specific attack rates

Meningococcal Vaccine Revaccination

- Revaccination may be indicated for persons at increased risk for infection*
- Revaccination may be considered 5 years after receipt of the MPSV
- MCV is recommended for revaccination of persons 11-55 years of age although use of MPSV is acceptable
- Revaccination after receipt of MCV is not recommended at this time

*e.g., aeplenic pereons and those who reside in areas in which disease is endemic (does not include college settings)

Adverse Reactions Following Vaccination

Meningococcal Polysaccharide Vaccine

Adverse reactions to MPSV are generally mild. The most frequent are **local reactions**, such as pain and redness at the injection site. These reactions last for 1–2 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 Conjugate Vaccine

Reported adverse reactions following MCV are similar to those reported after MPSV. 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

Meningococcal Vaccines Adverse Reactions

	MPSV	MCV
• Local reactions for 1-2 days	4%-48%	11%-59%
• Fever ≥100°F	3%	5%
• Systemic reactions (headache, malaise fatigue)	3%-60%	4%-62%

with 7 days of vaccination. Less than 3% of recipients reported these systemic reactions as severe.

All severe adverse events that occur after receipt of any vaccine should be reported to the Vaccine Adverse Events Reporting System (VAERS). For information on reporting, see the VAERS website at http://www.vaers.hhs.gov.

Contraindications and Precautions to Vaccination

Meningococcal Vaccines Contraindications and Precautions

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

For both MCV and MPSV, 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 MPSV during pregnancy have not documented adverse effects among either pregnant women or newborns. No data are available on the safety of MCV during pregnancy. However, pregnancy is not considered to be a contraindication to either MPSV or MCV.

Vaccine Storage and Handling

Both MPSV and MCV 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 MPSV must be used within 30 minutes of reconstitution, and multidose vials must be discarded 10 days after reconstitution. MCV 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 workers 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 workers 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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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.

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 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

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.

Smallpox Pathogenesis

- Virus contact with oropharyngeal or respiratory mucosa
- Virus replication in regional lymph nodes
- Viremia on about 8th day of infection
- Virus replication in oral and pharyngeal mucosa and skin

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

Smallpox Clinical Presentations

- Variola major
  - severe illness
  - case-fatality rate of ≥30%
- Variola minor
  - less severe
  - case-fatality rate of ≤1%

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

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.

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.

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

Differential Diagnosis

The most important differentiating feature between smallpox and other rash illnesses is the presence of fever before rash onset

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**

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.

Differential Diagnosis

Smallpox	Varicella
• Severe, febrile prodrome	• Mild or no prodrome
• 1-4 days before rash	• Little or no fever
• ≥101°F	• No associated symptoms
• Other symptoms: –prostration –headache –backache –chills –abdominal pain –vomiting	

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.

Differential Diagnosis

Smallpox	Varicella
• Deep, hard lesions	• Superficial lesions
• Round, well circumscribed	• Not well circumscribed
• Confluent or umbilicated	• Confluence and umbilication not common
• Lesions at same stage of development	• Lesions at all stages of development

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).

Smallpox Major Criteria

- **Febrile prodrome 1-4 days before rash onset; fever of ≥101°F, and at least 1 additional symptom***
- **Rash lesions are deep, firm/hard, round and well circumscribed**
- **On any one part of the body lesions in same stage of development**

*Prostration, headache, backache, chills, vomiting or severe abdominal pain

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.

Smallpox Minor Criteria

- Greatest concentration of lesions on face and distal extremities
- Lesions first appear on oral mucosa/palate, face, or forearms
- Patient appears toxic or moribund
- Lesions evolve from macules to papules to pustules
- Lesions on palms and 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.

Risk of Smallpox by Clinical History and Examination

- High risk
  - — febrile prodrome
  - — classic smallpox lesions
  - — same stage of development
- Moderate risk
  - — febrile prodrome
  - — 1 major OR ≥4 minor criteria
- Low risk
  - —no febrile prodrome
  - —febrile prodrome and <4 minor criteria

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.

Laboratory Confirmation

- Rapid diagnostic testing for varicella zoster virus (DFA, IFA, PCR)
- Electron microscopy (may identify *Orthopoxvirus* but not specific for variola)
- Culture
- Nucleic acid-based testing
- Serologic testing

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.

Smallpox Medical Management

- Notify public health authorities immediately for suspected case
- Strict respiratory and contact isolation
- Supportive care
- Antiviral agents?

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.

Smallpox

Smallpox Epidemiology

• Reservoir	Human (before eradication)
• Transmission	Respiratory by large particles Can be airborne
• Communicability	From onset of rash until all crusts separate

Smallpox Epidemiology

- Most transmission results from face-to-face contact with infected person (household and hospital contacts)
- Transmission most frequent during first week of rash

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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.

Smallpox Eradication

- Intensified Global Eradication program begun in 1966
- Initial strategy was mass vaccination
- Strategy evolved to "surveillance and containment"
- Last indigenous case in Somalia in October 1977

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.

Smallpox Vaccine

1796	Edward Jenner develops vaccine
1805	Use of cows to produce vaccine
1940s	Freeze-drying technology
1965	Licensure of bifurcated needle
1972	Routine vaccination stopped in U.S.
1983	Vaccine removed from civilian market

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.

Smallpox Vaccine

- Live vaccinia virus in calf lymph
- Contains trace amounts of polymyxin B, streptomycin, tetracycline, and neomycin
- Diluent contains glycerin and phenol
- New vaccine produced using cell culture technology does not contain antibiotics

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.

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

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

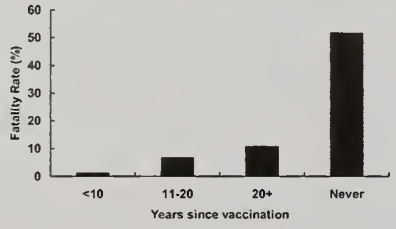
Smallpox Vaccine Efficacy

- 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;125:161-9.

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 postvaccinial 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.

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 (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

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.

Smallpox Response Plan

- Key elements:
  - —surveillance and investigation of cases
  - —contact tracing
  - —isolation guidelines
  - —specimen collection and handling
  - —communications
  - —decontamination

Smallpox Response Teams

- Emergency, healthcare workers and other critical personnel may be asked to volunteer to receive the vaccine
- Department of Defense will also vaccinate certain personnel who are or may be deployed in high threat areas
- Some personnel assigned to certain overseas embassies may be offered vaccination
- Does not include a recommendation for vaccination of the general public

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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

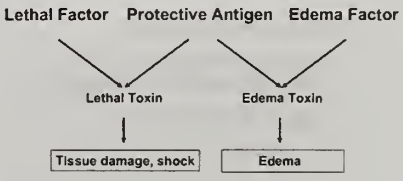
B. anthracis is a large aerobic, spore-forming, gram-positive bacillus that grows well on common culture media, such as blood agar. Stained *B. anthracis* from culture media appears as long parallel chains of organisms with square ends, referred to as "boxcars." *B. anthracis* spores can remain viable 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.

Anthrax Pathogenesis

- Spores enters through broken skin or mucous membranes
- Germinate in macrophages, replicate in lymph nodes and intracellular space
- Bacteria produce antiphagocytic capsule
- Production of toxins cause tissue destruction and edema

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.

Anthrax Pathogenesis

- Inhaled spores may reside in alveoli without germination for weeks
- Antibiotics effective against vegetative form but not spores
- Disease may develop after antibiotics discontinued
- Delayed onset not described for cutaneous or gastrointestinal forms

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.

Anthrax Clinical Features

- Three clinical forms
  - —cutaneous (most common in natural exposure situations)
  - —gastrointestinal (rare)
  - —inhalation

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

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.

Anthrax Laboratory Diagnosis

- Gram stain of clinical samples (skin lesion, blood, pleural fluid, CSF)
- Culture
- Adjunct Assays
  - –PCR
  - –serology (PA-based ELISA)
  - –immunohistochemistry

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.

Anthrax Medical Management

- **Antibiotics**
  - —ciprofloxacin or doxycycline and >1 additional drug active against *B. anthracis**
  - —IV, then PO
  - —30-60 days duration
- **Aggressive supportive care**

* rifampin, vancomycin, penicillin, ampicillin, chloramphenicol, imipenem, clindamycin, clarithromycin

Anthrax

Anthrax Epidemiology

• Reservoir	Infected animals, soil
• Transmission	Direct contact (cutaneous) Ingestion (gastrointestinal) Inhalation
• Temporal pattern	None
• Communicability	Not communicable (inhalation) Very rare (cutaneous)

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

Anthrax Epidemiology
Persons at Risk

- Agricultural exposure to animals (rare)
- Laboratorians exposed to *B. anthracis* spores (rare)
- Processors of wool, hair, hides, bones or other animal products (extremely rare)
- Biological terrorism

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.

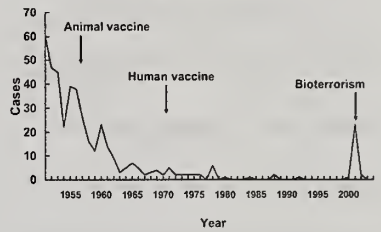
Communicability

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.

Anthrax—United States, 1951-2004



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

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 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

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*.

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)

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.

Vaccination Schedule and Use

Primary vaccination with AVA consists of three subcutaneous (SC) injections at 0, 2, and 4 weeks, followed by

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

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

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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.

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.

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

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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APPENDIX A
Schedules and Recommendations

Appendix A

Immunization Schedules on the Web

Childhood and Adolescent Immunization Schedule

Schedule: http://www.cdc.gov/nip/recs/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:

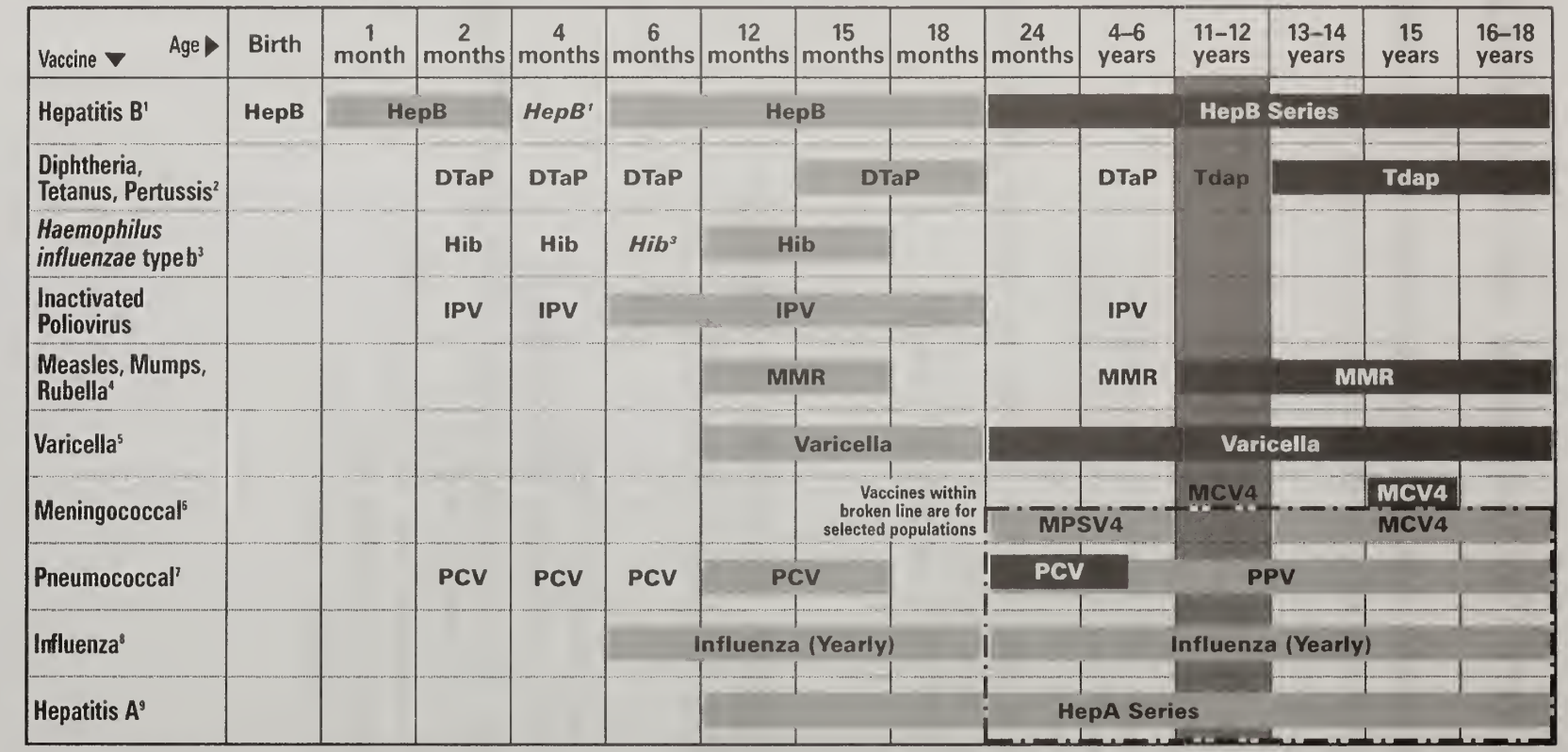
http://www.cdc.gov/nip/recs/adult-schedule.htm

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 . . .

DEPARTMENT OF HEALTH AND HUMAN SERVICES • CENTERS FOR DISEASE CONTROL AND PREVENTION

Recommended Childhood and Adolescent Immunization Schedule UNITED STATES • 2006



This schedule indicates the recommended ages for routine administration of currently licensed childhood vaccines, as of December 1, 2005, for children through age 18 years. Any dose not administered at the recommended age should be administered at any subsequent visit when indicated and feasible. ■ Indicates age groups that warrant special effort to administer those vaccines not previously administered. Additional vaccines may be licensed and recommended during the year. Licensed combination vaccines may be used whenever any components of the combination are indicated and other components of the vaccine are not contraindicated and if approved by the Food and Drug Administration for that dose of the series. Providers should consult the respective ACIP statement for detailed recommendations. 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 **www.vaers.hhs.gov** or by telephone, **800-822-7967**.

■ Range of recommended ages ■ Catch-up immunization ■ 11–12 year old assessment

1. **Hepatitis B vaccine (HepB).** ***AT BIRTH:*** **All newborns** should receive monovalent HepB soon after birth and before hospital discharge. **Infants born to mothers who are HBsAg-positive** should receive HepB and 0.5 mL of hepatitis B immune globulin (HBIG) within 12 hours of birth. **Infants born to mothers whose HBsAg status is unknown** should receive HepB within 12 hours of birth. The mother should have blood drawn as soon as possible to determine her HBsAg status; if HBsAg-positive, the infant should receive HBIG as soon as possible (no later than age 1 week). **For infants born to HBsAg-negative mothers,** the birth dose can be delayed in rare circumstances but only if a physician's order to withhold the vaccine and a copy of the mother's original HBsAg-negative laboratory report are documented in the infant's medical record. ***FOLLOWING THE BIRTHDOSE:*** The HepB series should be completed with either monovalent HepB or a combination vaccine containing HepB. The second dose should be administered at age 1–2 months. The final dose should be administered at age ≥24 weeks. It is permissible to administer 4 doses of HepB (e.g., when combination vaccines are given after the birth dose); however, if monovalent HepB is used, a dose at age 4 months is not needed. **Infants born to HBsAg-positive mothers** should be tested for HBsAg and antibody to HBsAg after completion of the HepB series, at age 9–18 months (generally at the next well-child visit after completion of the vaccine series).
2. **Diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP).** The fourth dose of DTaP may be administered as early as age 12 months, provided 6 months have elapsed since the third dose and the child is unlikely to return at age 15–18 months. The final dose in the series should be given at age ≥4 years.

   Tetanus and diphtheria toxoids and acellular pertussis vaccine (Tdap – adolescent preparation) is recommended at age 11–12 years for those who have completed the recommended childhood DTP/DTaP vaccination series and have not received a Td booster dose. Adolescents 13–18 years who missed the 11–12-year Td/Tdap booster dose should also receive a single dose of Tdap if they have completed the recommended childhood DTP/DTaP vaccination series. Subsequent **tetanus and diphtheria toxoids (Td)** are recommended every 10 years.
3. ***Haemophilus influenzae*** **type b conjugate vaccine (Hib).** Three Hib conjugate vaccines are licensed for infant use. If PRP-OMP (PedvaxHIB® or ComVax® [Merck]) is administered at ages 2 and 4 months, a dose at age 6 months is not required. DTaP/Hib combination products should not be used for primary immunization in infants at ages 2, 4 or 6 months but can be used as boosters after any Hib vaccine. The final dose in the series should be administered at age ≥12 months.
4. **Measles, mumps, and rubella vaccine (MMR).** The second dose of MMR is recommended routinely at age 4–6 years but may be administered during any visit, provided at least 4 weeks have elapsed since the first dose and both doses are administered beginning at or after age 12 months. Those who have not previously received the second dose should complete the schedule by age 11–12 years.
5. **Varicella vaccine.** Varicella vaccine is recommended at any visit at or after age 12 months for susceptible children (i.e., those who lack a reliable history of chickenpox). Susceptible persons aged ≥13 years should receive 2 doses administered at least 4 weeks apart.
6. **Meningococcal vaccine (MCV4).** Meningococcal conjugate vaccine (MCV4) should be given to all children at the 11–12 year old visit as well as to unvaccinated adolescents at high school entry (15 years of age). Other adolescents who wish to decrease their risk for meningococcal disease may also be vaccinated. All college freshmen living in dormitories should also be vaccinated, preferably with MCV4, although **meningococcal polysaccharide vaccine (MPSV4)** is an acceptable alternative. Vaccination against invasive meningococcal disease is recommended for children and adolescents aged ≥2 years with terminal complement deficiencies or anatomic or functional asplenia and certain other high risk groups (see *MMWR* 2005;54 [RR-7]:1-21); use MPSV4 for children aged 2–10 years and MCV4 for older children, although MPSV4 is an acceptable alternative.
7. **Pneumococcal vaccine.** The heptavalent **pneumococcal conjugate vaccine (PCV)** is recommended for all children aged 2–23 months and for certain children aged 24–59 months. The final dose in the series should be given at age ≥12 months. **Pneumococcal polysaccharide vaccine (PPV)** is recommended in addition to PCV for certain high-risk groups. See *MMWR* 2000; 49(RR-9):1-35.
8. **Influenza vaccine.** Influenza vaccine is recommended annually for children aged ≥6 months with certain risk factors (including, but not limited to, asthma, cardiac disease, sickle cell disease, human immunodeficiency virus [HIV], diabetes, and conditions that can compromise respiratory function or handling of respiratory secretions or that can increase the risk for aspiration), healthcare workers, and other persons (including household members) in close contact with persons in groups at high risk (see *MMWR* 2005;54[RR-8]:1-55). In addition, healthy children aged 6–23 months and close contacts of healthy children aged 0–5 months are recommended to receive influenza vaccine because children in this age group are at substantially increased risk for influenza-related hospitalizations. For healthy persons aged 5–49 years, the intranasally administered, live, attenuated influenza vaccine (LAIV) is an acceptable alternative to the intramuscular trivalent inactivated influenza vaccine (TIV). See *MMWR* 2005;54(RR-8):1-55. Children receiving TIV should be administered a dosage appropriate for their age (0.25 mL if aged 6–35 months or 0.5 mL if aged ≥3 years). Children aged ≤8 years who are receiving influenza vaccine for the first time should receive 2 doses (separated by at least 4 weeks for TIV and at least 6 weeks for LAIV).
9. **Hepatitis A vaccine (HepA).** HepA is recommended for all children at 1 year of age (i.e., 12–23 months). The 2 doses in the series should be administered at least 6 months apart. States, counties, and communities with existing HepA vaccination programs for children 2–18 years of age are encouraged to maintain these programs. In these areas, new efforts focused on routine vaccination of 1-year-old children should enhance, not replace, ongoing programs directed at a broader population of children. HepA is also recommended for certain high risk groups (see *MMWR* 1999; 48[RR-12]1-37).

The Childhood and Adolescent Immunization Schedule is approved by:
Advisory Committee on Immunization Practices www.cdc.gov/nip/acip • American Academy of Pediatrics www.aap.org • American Academy of Family Physicians www.aafp.org

Recommended Immunization Schedule for Children and Adolescents Who Start Late or Who Are More Than 1 Month Behind

UNITED STATES • 2006

The tables below give catch-up schedules and minimum intervals between doses for children who have delayed immunizations. There is no need to restart a vaccine series regardless of the time that has elapsed between doses. Use the chart appropriate for the child's age.

CATCH-UP SCHEDULE FOR CHILDREN AGED 4 MONTHS THROUGH 6 YEARS

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
Diphtheria, Tetanus, Pertussis	6 wks	4 weeks	4 weeks	6 months	6 months[1]
Inactivated Poliovirus	6 wks	4 weeks	4 weeks	4 weeks[2]	
Hepatitis B[3]	Birth	4 weeks	8 weeks (and 16 weeks after first dose)		
Measles, Mumps, Rubella	12 mo	4 weeks[4]			
Varicella	12 mo				
Haemophilus influenzae type b[5]	6 wks	4 weeks if first dose given at age <12 months 8 weeks (as final dose) if first dose given at age 12-14 months No further doses needed if first dose given at age ≥15 months	4 weeks[6] if current age <12 months 8 weeks (as final dose)[6] if current age ≥12 months and second dose given at age <15 months No further doses needed if previous dose given at age ≥15 mo	8 weeks (as final dose) This dose only necessary for children aged 12 months–5 years who received 3 doses before age 12 months	
Pneumococcal[7]	6 wks	4 weeks if first dose given at age <12 months and current age <24 months 8 weeks (as final dose) if first dose given at age ≥12 months or current age 24–59 months No further doses needed for healthy children if first dose given at age ≥24 months	4 weeks if current age <12 months 8 weeks (as final dose) if current age ≥12 months No further doses needed for healthy children if previous dose given at age ≥24 months	8 weeks (as final dose) This dose only necessary for children aged 12 months–5 years who received 3 doses before age 12 months	

CATCH-UP SCHEDULE FOR CHILDREN AGED 7 YEARS THROUGH 18 YEARS			
Vaccine	Minimum Interval Between Doses		
	Dose 1 to Dose 2	Dose 2 to Dose 3	Dose 3 to Booster Dose
Tetanus, Diphtheria[8]	**4 weeks**	**6 months**	**6 months** if first dose given at age <12 months and current age <11 years; otherwise **5 years**
Inactivated Poliovirus[9]	**4 weeks**	**4 weeks**	IPV[2,9]
Hepatitis B	**4 weeks**	**8 weeks** (and 16 weeks after first dose)	
Measles, Mumps, Rubella	**4 weeks**		
Varicella[10]	**4 weeks**		

1. **DTaP.** The fifth dose is not necessary if the fourth dose was administered after the fourth birthday.
2. **IPV.** For children who received an all-IPV or all-oral poliovirus (OPV) series, a fourth dose is not necessary if third dose was administered at age ≥4 years. If both OPV and IPV were administered as part of a series, a total of 4 doses should be given, regardless of the child's current age.
3. **HepB.** Administer the 3-dose series to all children and adolescents<19 years of age if they were not previously vaccinated.
4. **MMR.** The second dose of MMR is recommended routinely at age 4–6 years but may be administered earlier if desired.
5. **Hib.** Vaccine is not generally recommended for children aged ≥5 years.
6. **Hib.** If current age <12 months and the first 2 doses were PRP-OMP (PedvaxHIB® or ComVax® [Merck]), the third (and final) dose should be administered at age 12–15 months and at least 8 weeks after the second dose.
7. **PCV.** Vaccine is not generally recommended for children aged ≥5 years.
8. **Td.** Adolescent tetanus, diphtheria, and pertussis vaccine (Tdap) may be substituted for any dose in a primary catch-up series or as a booster if age appropriate for Tdap. A five-year interval from the last Td dose is encouraged when Tdap is used as a booster dose. See ACIP recommendations for further information.
9. **IPV.** Vaccine is not generally recommended for persons aged ≥18 years.
10. **Varicella.** Administer the 2-dose series to all susceptible adolescents aged ≥13 years.

Report adverse reactions to vaccines through the federal Vaccine Adverse Event Reporting System. For information on reporting reactions following immunization, please visit www.vaers.hhs.gov or call the 24-hour national toll-free information line 800-822-7967. Report suspected cases of vaccine-preventable diseases to your state or local health department.

For additional information about vaccines, including precautions and contraindications for immunization and vaccine shortages, please visit the National Immunization Program Website at www.cdc.gov/nip or contact 800-CDC-INFO (800-232-4636) (In English, En Español — 24/7)

Recommended Adult Immunization Schedule, by Vaccine and Age Group

UNITED STATES, OCTOBER 2005–SEPTEMBER 2006

Vaccine ▼ / Age group ▶	19–49 years	50–64 years	≥ 65 years
Tetanus, diphtheria (Td)[1]*	1-dose booster every 10 yrs		
Measles, mumps, rubella (MMR)[2]*	1or 2 doses	1 dose	
Varicella[3]*	2 doses (0, 4–8 wks)	2 doses (0, 4–8 wks)	
Vaccines below broken line are for selected populations			
Influenza[4]*	1 dose annually	1 dose annually	
Pneumococcal (polysaccharide)[5,6]	1–2 doses		1 dose
Hepatitis A[7]*	2 doses (0, 6–12 mos, or 0, 6–18 mos)		
Hepatitis B[8]*	3 doses (0, 1–2, 4–6 mos)		
Meningococcal[9]	1 or more doses		

NOTE: These recommendations must be read along with the footnotes.

*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., based on medical, occupational, lifestyle, or other indications)

This schedule indicates the recommended age groups and medical indications for routine administration of currently licensed vaccines for persons aged ≥19 years. 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, consult the manufacturers' package inserts and the complete statements from the ACIP ( ).

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 by telephone, 800-822-7967, or from the VAERS website at .

Information on how to file a Vaccine Injury Compensation Program claim is available at 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 listed above and contraindications for vaccination is also available at or from the CDC-INFO Contact Center at 800-CDC-INFO (232-4636) in English and Spanish, 24 hours a day, 7 days a week.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

CDC

Recommended Adult Immunization Schedule, by Vaccine and Medical and Other Indications

UNITED STATES, OCTOBER 2005–SEPTEMBER 2006

Vaccine ▼ / Indication ▶	Pregnancy	Congenital immunodoficiency; leukemia;[10] lymphoma; generalized malignancy; cerebrospinal fluid leaks; therapy with alkylating agents, antimetabolites, radiation, or high-dose, long-term corticosteroids	Diabetes; heart disease; chronic pulmonary disease; chronic liver disease, including chronic alcoholism	Asplenia[10] (including elective splenectomy and terminal complement component deficiencies)	Kidney failure, end-stage renal disease, recipients of hemodialysis or clotting factor concentrates	Human immunodeficiency virus (HIV) infection[2,10]	Healthcare workers
Tetanus, diphtheria (Td)[1]*	1-dose booster every 10 yrs						
Measles, mumps, rubella (MMR)[2]*			1 or 2 doses				
Varicella[3]*			2 doses (0, 4–8 wks)				2 doses
Influenza[4]*	1 dose annually			1 dose annually			
Pneumococcal (polysaccharide)[5,6]	1–2 doses	1–2 doses					1–2 doses
Hepatitis A[7]*	2 doses (0, 6–12 mos, or 0, 6–18 mos)						
Hepatitis B[8]*	3 doses (0, 1–2, 4–6 mos)				3 doses (0, 1–2, 4–6 mos)		
Meningococcal[9]	1 dose			1 dose	1 dose		

NOTE: These recommendations must be read along with the footnotes.

*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., based on medical, occupational, lifestyle, or other indications)

Contraindicated

Approved by the Advisory Committee on Immunization Practices (ACIP), the American College of Obstetricians and Gynecologists (ACOG), and the American Academy of Family Physicians (AAFP)

Footnotes

Recommended Adult Immunization Schedule, UNITED STATES, OCTOBER 2005–SEPTEMBER 2006

1. **Tetanus and Diphtheria (Td) vaccination.** Adults with uncertain histories of a complete primary vaccination series with diphtheria and tetanus toxoid-containing vaccines should receive a primary series using combined Td toxoid. A primary series for adults is 3 doses; administer the first 2 doses at least 4 weeks apart and the third dose 6–12 months after the second. Administer 1 dose if the person received the primary series and if the last vaccination was received ≥10 years previously. Consult ACIP statement for recommendations for administering Td as prophylaxis in wound management (www.cdc.gov/mmwr/preview/mmwrhtml/00038745.htm). The American College of Physicians Task Force on Adult Immunization supports a second option for Td use in adults: a single Td booster at age 50 years for persons who have completed the full pediatric series, including the teenage/young adult booster. A newly licensed tetanus-diphtheria-acellular pertussis vaccine is available for adults. ACIP recommendations for its use will be published.
2. **Measles, Mumps, Rubella (MMR) vaccination.** *Measles component:* adults born before 1957 can be considered immune to measles. Adults born during or after 1957 should receive ≥1 dose of MMR unless they have a medical contraindication, documentation of ≥1 dose, history of measles based on healthcare provider diagnosis, or laboratory evidence of immunity. A second dose of MMR is recommended for adults who 1) were recently exposed to measles or in an outbreak setting, 2) were previously vaccinated with killed measles vaccine, 3) were vaccinated with an unknown type of measles vaccine during 1963–1967, 4) are students in postsecondary educational institutions, 5) work in a healthcare facility, or 6) plan to travel internationally. Withhold MMR or other measles-containing vaccines from HIV-infected persons with severe immunosuppression. *Mumps component:* 1 dose of MMR vaccine should be adequate for protection for those born during or after 1957 who lack a history of mumps based on healthcare provider diagnosis or who lack laboratory evidence of immunity. *Rubella component:* administer 1 dose of MMR vaccine to women whose rubella vaccination history is unreliable or who lack laboratory evidence of immunity. For women of childbearing age, regardless of birth year, routinely determine rubella immunity and counsel women regarding congenital rubella syndrome. Do not vaccinate women who are pregnant or might become pregnant within 4 weeks of receiving the vaccine. Women who do not have evidence of immunity should receive MMR vaccine upon completion or termination of pregnancy and before discharge from the healthcare facility.
3. **Varicella vaccination.** Varicella vaccination is recommended for all adults without evidence of immunity to varicella. Special consideration should be given to those who 1) have close contact with persons at high risk for severe disease (healthcare workers and family contacts of immunocompromised persons) or 2) are at high risk for exposure or transmission (e.g., teachers of young children; 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) documented age-appropriate varicella vaccination (i.e., receipt of 1 dose before age 13 years or receipt of 2 doses [administered at least 4 weeks apart] after age 13 years); 2) born in the United States before 1966; 3) history of varicella disease based on healthcare provider diagnosis or self- or parental report of typical varicella disease for non–U.S.-born persons born before 1966 and all persons born during 1966–1997 (for a patient reporting a history of an atypical, mild case, healthcare providers should seek either an epidemiologic link with a typical varicella case or evidence of laboratory confirmation, if it was performed at the time of acute disease); 4) history of herpes zoster based on healthcare provider diagnosis; or 5) laboratory evidence of immunity. Do not vaccinate women who are pregnant or might become pregnant within 4 weeks of receiving the vaccine. Assess pregnant women for evidence of varicella immunity. Women who do not have evidence of immunity should receive dose 1 of varicella vaccine upon completion or termination of pregnancy and before discharge from the healthcare facility. Dose 2 should be given 4–8 weeks after dose 1.
4. **Influenza vaccination.** *Medical indications:* chronic disorders of the cardiovascular or pulmonary systems, including asthma; chronic metabolic diseases, including diabetes mellitus, renal dysfunction, hemoglobinopathies, or immunosuppression (including immunosuppression caused by medications or by HIV); any condition (e.g., cognitive dysfunction, spinal cord injury, seizure disorder or other neuromuscular disorder) that compromises respiratory function or the handling of respiratory secretions or that can increase the risk of aspiration; 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:* healthcare workers and employees of long-term care and assisted living facilities. *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 (i.e., in-home household contacts and caregivers of children birth through 23 months of age, or persons of all ages with high-risk conditions); and anyone who wishes to be vaccinated.

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Recommended Adult Immunization Schedule, UNITED STATES, OCTOBER 2005–SEPTEMBER 2006

For healthy nonpregnant persons aged 5–49 years without high-risk conditions who are not contacts of severely immunocompromised persons in special care units, intranasally administered influenza vaccine (FluMist®) may be administered in lieu of inactivated vaccine.

5. **Pneumococcal polysaccharide vaccination.** *Medical indications:* chronic disorders of the pulmonary system (excluding asthma); cardiovascular diseases; diabetes mellitus; chronic liver diseases, including liver disease as a result of alcohol abuse (e.g.,cirrhosis); 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]); immunosuppressive conditions (e.g., congenital immunodeficiency, HIV infection [vaccinate as close to diagnosis as possible when CD4 cell counts are highest], leukemia, lymphoma, multiple myeloma, Hodgkin disease, generalized malignancy, organ or bone marrow transplantation); chemotherapy with alkylating agents, antimetabolites, or high-dose, long-term corticosteroids; and cochlear implants. *Other indications:* Alaska Natives and certain American Indian populations; residents of nursing homes and other long-term care facilities.
6. **Revaccination with pneumococcal polysaccharide vaccine.** 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); immunosuppressive conditions (e.g., congenital immunodeficiency, HIV infection, leukemia, lymphoma, multiple myeloma, Hodgkin disease, generalized malignancy, organ or bone marrow transplantation); or chemotherapy with alkylating agents, antimetabolites, or high-dose, long-term corticosteroids. For persons aged ≥65 years, one-time revaccination if they were vaccinated ≥5 years previously and were aged <65 years at the time of primary vaccination.
7. **Hepatitis A vaccination.** *Medical indications:* persons with clotting factor disorders or chronic liver disease. *Behavioral indications:* men who have sex with men or users of 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 (for list of countries, visit www.cdc.gov/travel/diseases.htm#heparit) as well as any person wishing to obtain immunity. Current vaccines should be given in a 2-dose series at either 0 and 6–12 months, or 0 and 6–18 months. If the combined hepatitis A and hepatitis B vaccine is used, administer 3 doses at 0, 1, and 6 months.
8. **Hepatitis B vaccination.** *Medical indications:* hemodialysis patients (use special formulation [40 μg/mL] or two 20-μg/mL doses) or patients who receive clotting factor concentrates. *Occupational indications:* healthcare workers and public-safety workers who have exposure to blood in the workplace; and persons in training in schools of medicine, dentistry, nursing, laboratory technology, and other allied health professions. *Behavioral indications:* injection-drug users; persons with more than one sex partner in the previous 6 months; persons with a recently acquired sexually transmitted disease (STD); 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 of institutions for the developmentally disabled; all clients of STD clinics; inmates of correctional facilities; or international travelers who will be in countries with high or intermediate prevalence of chronic HBV infection for >6 months (for list of countries, visit www.cdc.gov/travel/diseases.htm#hepb).
9. **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 reside in countries in which meningococcal disease is hyperendemic or epidemic (e.g., the "meningitis belt" of sub-Saharan Africa during the dry season [Dec–June]), particularly if contact with the 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 vaccine is preferred for adults meeting any of the above indications who are aged ≤55 years, although meningococcal polysaccharide vaccine (MPSV4) is an acceptable alternative. Revaccination after 5 years may be indicated for adults previously vaccinated with MPSV4 who remain at high risk for infection (e.g., persons residing in areas in which disease is epidemic).
10. **Selected conditions for which *Haemophilus influenzae* type b (Hib) vaccine may be used.** *Haemophilus influenzae* type b conjugate vaccines are licensed for children aged 6 weeks–71 months. No efficacy data are available on which to base a recommendation concerning 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, leukemia, or HIV infection, or have had splenectomies; administering vaccine to these patients is not contraindicated.

Approved by the Advisory Committee on Immunization Practices (ACIP), the American College of Obstetricians and Gynecologists (ACOG), and the American Academy of Family Physicians (AAFP)

Appendix A

Recommended and minimum ages and intervals between vaccine doses*

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-1†	Birth	Birth	1-4 months	4 weeks
Hepatitis B-2	1-4 months	4 weeks	2-17 months	8 weeks
Hepatitis B-3§	6-18 months	24 weeks	–	–
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 vaccine (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 vaccine (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	–	–
MMR-1§§	12-15 months ¶¶	12 months	3-5 years	4 weeks
MMR-2§§	4-6 years	13 months	–	–
Varicella ‡‡	12-18 months	12 months	4 weeks ‡‡	4 weeks ‡‡
Hepatitis A-1	12-23 months	12 months	6-18 months¶	6 months¶
Hepatitis A-2	18-41 months	18 months	–	–
Influenza Vaccine (TIV)***	6-23 months	6 months	1 month	4 weeks
Influenza Vaccine (LAIV)***	–	5 years	6-10 weeks	6 weeks
Meningococcal Conjugate Vaccine (MCV)	11-12 years	11 years	–	–
Meningococcal Polysaccharide Vaccine (MPSV)-1	–	2 years	5 years	5 years
MPSV-2	–	7 years †††	–	–
Tdap/Td §§§	≥11 years	11 years	10 years	5 years
Pneumococcal polysaccharide vaccine (PPV)-1	–	2 years	5 years	5 years
PPV-2	–	7 years ¶¶	–	–

DTaP = Diphtheria and tetanus toxoids and acellular pertussis vaccine
MMR = Measles, mumps and rubella
TIV = Trivalent (inactivated) influenza vaccine
LAIV = Live, attenuated (intranasal) influenza vaccine
Td = Tetanus and reduced diphtheria toxoids.
Tdap = Tetanus toxoid, reduced diphtheria toxoid, and reduced acellular pertussis vaccine

* Combination vaccines are available. Using 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];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.

† Combination vaccines containing the Hepatitis B component are available (HepB-Hib, DTaP-HepB-IPV, HepA-HepB). These vaccines should not be administered to infants less than 6 weeks old because of the other components (i.e., Hib, DTaP, IPV, and HepA).

§ Hepatitis B-3 should be administered at least 8 weeks after Hepatitis B-2 and at least 16 weeks after Hepatitis B-1, and it 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 needn't 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 or older require fewer doses to complete the series (see CDC. Haemophilus b conjugate vaccines for prevention of *Haemophilus influenzae*, type b disease among infants and children two months of age and older: recommendations of the ACIP. *MMWR* 1991; 40[No. RR-1]:1-7, and CDC. Preventing pneumococcal disease among infants and young children: recommendations of the Advisory Committee on Immunization Practices [ACIP], *MMWR* 2000; 49[No. RR-9];1-35).

†† For a regimen of o*nly* PRP-OMP (Pedvax-Hib®, manufactured by Merck), a dose administered at age 6 months is not required.

§§ Combination MMR-varicella can be used if the child is younger than 13 years old. Also see footnote ‡‡.

¶¶ During a measles outbreak, if cases are occurring among infants younger than 12 months of age, measles vaccination of infants aged 6 months and older can be undertaken as an outbreak control measure. However, doses administered before the first birthday 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]:1-57).

‡‡ Children aged 12 months through 12 years require only one dose of varicella vaccine. Persons aged 13 years and older should receive two doses separated by at least 4 weeks. Children younger than 13 years old can receive a second dose of varicella vaccine during a varicella outbreak if it has been 3 months or more since the first dose.

*** Two doses of influenza vaccine are recommended for children younger than 9 years of age who are receiving the vaccine for the first time. Children younger than 9 years who have previously received influenza vaccine, and persons 9 years of age and older, require only one dose per influenza season.

††† A second dose of meningococcal vaccine is recommended for people previously vaccinated with MPSV who remain at high risk of meningococcal disease. MCV is preferred when revaccinating persons aged 11-55 years, but a second dose of MPSV is acceptable. (Prevention and Control of Meningococcal Disease Recommendations of the Advisory Committee on Immunization Practices [ACIP]. *MMWR* 2005; 54: RR-07.)

§§§ Only one dose of Tdap is recommended. Subsequent doses should be given as Td. If vaccination to prevent tetanus and/or diphtheria disease is required during the ages 7 through 10 years, Td should be given (minimum age for Td is 7 years). The preferred interval between Tdap and a previous dose of Td is 5 years. For management of a tetanus-prone wound, the minimum interval after a previous dose of any tetanus-containing vaccine is 5 years.

¶¶¶ A second doses 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 younger than 10 years of age at the time of revaccination. (See CDC. Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunization Practices [ACIP]. *MMWR* 1997;46[No. RR-8]:1-24).

Adapted from Table 1, ACIP General Recommendations on Immunization: *MMWR* 2002;51(No. RR-2) **January 2006**

Summary of Recommendations for Childhood and Adolescent Immunization

Adapted from the recommendations of the Advisory Committee on Immunization Practices (ACIP)* by the Immunization Action Coalition, November 2005

Vaccine name and route	Schedule for routine vaccination and other guidelines (any vaccine can be given with another)	Schedule for catch-up vaccination and other related issues	Contraindications and precautions (mild illness is not a contraindication)
Hepatitis B *Give IM*	• Vaccinate all children 0 through 18yrs of age. • Vaccinate all newborns with monovalent vaccine prior to hospital discharge. Give dose #2 at 1–2m and the final dose at 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 (2m, 4m, 12–15m of age) or Pediarix (2m, 4m, 6m of age). It is acceptable to give 4 doses of hepatitis B vaccine to infants. • **If mother is HBsAg-positive:** give the newborn HBIG + dose #1 within 12hrs of birth, #2 at 1–2m, and #3 at 6m of age. • **If mother's HBsAg status is unknown:** give the newborn dose #1 within 12hrs of birth, #2 at 1–2m, and #3 at 6m of age. If mother is subsequently found to be HBsAg positive, give infant HBIG within 7d of birth.	• Do not restart series, no matter how long since previous dose. • 3-dose series can be started at any age. • Minimum spacing for children and teens: 4wks between #1 & #2, and 8wks between #2 & #3. Overall there must be at least 16wks between #1 & #3 (e.g., 0-, 2-, 4m; 0-, 1-, 4m). **Special Notes on Hepatitis B Vaccine** **Dosing of hepatitis B vaccines:** Vaccine brands are interchangeable for 3-dose schedules. For persons 0 through 19yrs of age, 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 1.0mL (adult formulation) spaced 4–6m apart. (Engerix-B is not licensed for a 2-dose schedule.) **For premature infants:** Consult *2003 AAP Red Book* (p. 66–68) as hepatitis B vaccination recommendations for premies may differ from routine infant schedule.	**Contraindication** Previous anaphylactic reaction to this vaccine or to any of its components. **Precaution** Moderate or severe acute illness.
DTaP (Diphtheria, tetanus, acellular pertussis) *Give IM*	• Give to children at 2m, 4m, 6m, 15–18m, 4–6yrs of age. • May give dose #1 as early as 6wks of age. • May give #4 as early as 12m of age if 6m have elapsed since #3 and the child is unlikely to return at age 15–18m. • Do not give DTaP to children age 7yrs and older. • It is preferable but not mandatory to use the same DTaP product for all doses.	• #2 & #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 (4–6yrs of age). • If #4 is given after 4th birthday, #5 is not needed.	**Contraindications** • Previous anaphylactic or neurologic reaction to this vaccine or to any of its components. • Previous encephalopathy within 7d after DTP or DTaP. This is a contraindication for DTaP only (not DT). **Precaution** Moderate or severe acute illness. **Precautions for DTaP** • Any of these occurrences within 48hrs after previous dose: 1) temperature of 105°F (40.5°C) or higher; 2) continuous crying 3hrs or more; or 3) pale or limp episode or collapse. • Convulsion within 3d of previous DTaP/DTP. • Unstable progressive neurologic problem (defer until stable).
DT *Give IM*	Give to children age 6yrs and younger if child had a serious reaction to "P" in DTaP/DTP or if parents refuse the pertussis component.		
Td (For **Tdap**, see note in next column) *Give IM*	• Give Td booster dose to children 11–12yrs of age if 5yrs have elapsed since last dose; then boost every 10yrs. Use Td, not tetanus toxoid (TT), for persons age 7yrs and older for all indications. **Note:** Two Tdap products, Boostrix (GSK) and Adacel (sanofi pasteur), were licensed by the FDA in 2005 for use in adolescents and/or adults. Provisional ACIP recommendations for Tdap use may be found at www.cdc.gov/nip/vaccine/tdap/tdap_acip_recs.pdf.	For unvaccinated patients: give dose #1 now, give 2nd dose 4wks later, give 3rd dose 6m after #2, then give booster every 10yrs.	**Contraindication** Previous anaphylactic or neurologic reaction to this vaccine or to any of its components. **Precautions** • Moderate or severe acute illness. • Guillain-Barré syndrome within 6wks after previous dose of tetanus toxoid-containing vaccine.
Polio (IPV) *Give SC or IM*	• Give to children at 2m, 4m, 6–18m, and 4–6yrs of age. • May give #1 as early as 6wks of age. • Not routinely recommended for those age18yrs 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 anaphylactic or neurologic reaction to this vaccine or to any of its components. **Precaution** Moderate or severe acute illness.

*For specific ACIP recommendations, refer to the official ACIP statements published in *MMWR*. To obtain copies of these statements, visit CDC's website at www.cdc.gov/nip/publications/ACIP-list.htm; or visit the Immunization Action Coalition (IAC) website at www.immunize.org/acip. Visit IAC's website at www.immunize.org/childrules to make sure you have the most current version. IAC thanks William Atkinson, MD, MPH, from CDC's National Immunization Program, and Linda Moyer, RN, from CDC's Division of Viral Hepatitis, for their assistance. For more information, contact IAC at 1573 Selby Avenue, St. Paul, MN 55104, (651) 647-9009, or email admin@immunize.org.

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 other related issues	Contraindications and precautions (mild illness is not a contraindication)
Varicella (Var) (Chickenpox) *Give SC*	• Give 1 dose to children at 12–18m of age. • Vaccinate all children age 12m and older including all adolescents who have not had chickenpox. • May use as postexposure prophylaxis if given within 3–5d. • If Var and MMR (and/or yellow fever vaccine) are not given on the same day, space them at least 28d apart.	• Do not give to children younger than age 12m. • Susceptible children age 12yrs and younger should receive 1 dose only. • Susceptible persons age 13yrs and older should receive 2 doses 4–8wks apart.	**Contraindications** • Previous anaphylactic reaction to this vaccine or to any of its components. • Pregnancy or possibility of pregnancy within 4 weeks. • Children immunocompromised because of high doses of systemic steroids, cancer, leukemia, lymphoma, or immunodeficiency. **Note:** For patients with humoral immunodeficiency, HIV infection, or leukemia, or for patients on high doses of systemic steroids, see ACIP recommendations. **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. • History of thrombocytopenia or thrombocytopenic purpura.
MMR (Measles, mumps, rubella) *Give SC*	• Give dose #1 at 12–15m of age. • Give dose #2 at 4–6yrs of age; although dose #2 may be given earlier if at least 4wks since dose #1. • If a dose was given before 12m of age, it doesn't count as the first dose, so give #1 at 12–15m of age with a minimum interval of 4wks between the invalid dose and dose #1. • If MMR and Var (and/or yellow fever vaccine) are not given on the same day, space them at least 28d apart.	• A dose should be given whenever the child is behind. Exception: If MMR and Var (and/or yellow fever vaccine) are not given on the same day, space them at least 28d apart. • Dose #2 can be given at any time if at least 28d have elapsed since dose #1 and both doses are administered after 1yr of age.	**Contraindications** • Previous anaphylactic reaction to this vaccine or to any of its components. • Pregnancy or possibility of pregnancy within 4 wks. • Severe immunodeficiency (e.g., hematologic & solid tumors; congenital immunodeficiency; long-term immunosuppressive therapy, or severely symptomatic HIV). **Precautions** • If blood, plasma, or immune globulin given in past 11m or if on high-dose immunosuppressive therapy, see ACIP statement *General Recommendations on Immunization* regarding delay time. • History of thrombocytopenia or thrombocytopenic purpura. **Note:** MMR is not contraindicated if a PPD test was recently applied. If PPD and MMR not given on same day, delay PPD for 4–6wks after MMR.
Influenza Trivalent inactivated influenza vaccine (TIV) *Give IM*	• On an annual basis, vaccinate all children and adolescents who -are 6–23m of age. -have a risk factor (e.g., pregnancy, heart disease, lung disease, diabetes, renal dysfunction, hemoglobinopathy, immunosuppression) or live in a chronic-care facility. -live or work with at-risk people as listed above. -are a household contact of a child 0–23m of age. • Any child wishing to reduce the likelihood of becoming ill with influenza may be vaccinated. • Give 2 doses to first-time vaccinees 6m–9yrs of age, separated by at least 4wks. • Give 0.25 mL dose to children 6–35m of age and 0.5 mL dose if age 3yrs and older.	If previously unvaccinated child age 8yrs and younger does not receive 2nd dose during initial vaccination season, give only 1 dose the following season.	**Contraindication** Previous anaphylactic reaction to this vaccine, to any of its components, or to eggs. **Precaution** Moderate or severe acute illness.
Live attenuated influenza vaccine (LAIV) *Give intranasally*	• May use LAIV in healthy children age 5yrs and older only. • Give 2 doses to first-time vaccinees 5–9yrs of age, separated by at least 6wks.		**Contraindications** • Previous anaphylactic reaction to this vaccine, to any of its components, or to eggs. • Pregnancy, asthma, reactive airway 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; a known or suspected immune deficiency disease or receiving immunosuppressive therapy; history of Guillain-Barré syndrome. **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 other related issues	Contraindications and precautions (mild illness is not a contraindication)
Hib (*Haemophilus influenzae* type b) *Give IM*	• HibTITER (HbOC) & ActHib (PRP-T): give at 2m, 4m, 6m, 12–15m (booster dose). • PedvaxHIB or Comvax (containing PRP-OMP): give at 2m, 4m, 12–15m. • Dose #1 of Hib vaccine may be given no earlier than 6wks of age. • The last dose (booster dose) is given no earlier than 12m of age and a minimum of 8wks after the previous dose. • Hib vaccines are interchangeable; however, if different brands of Hib vaccines are administered, a total of three 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 the ages of 15m up to 5yrs. **HibTITER and ActHib:** • #2 and #3 may be given 4 wks after previous dose. • If #1 was given at 7–11m, only 3 doses are needed; #2 is given 4–8wks after #1, then hoost at 12–15m (and must be at least 8wks after dose #2). **PedvaxHIB and Comvax:** • #2 may be given 4wks after dose #1.	**Contraindication** Previous anaphylactic reaction to this vaccine or to any of its components. **Precaution** Moderate or severe acute illness.
Pneumo. conjugate (PCV) *Give IM*	• Give at 2m, 4m, 6m, and 12–15m of age. • Dose #1 may be given as early as 6wks of age. • Give 1 dose to unvaccinated healthy children 24–59m of age. • Give 2 doses at least 8wks apart to unvaccinated high-risk children 24–59m of age. • 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 mellitus; CSF leak; HIV infection; or immunosuppression.	• Minimum interval between doses for infants younger than age 12m is 4wks, for age 12m and older is 8wks. • For infants 7–11m of age: If unvaccinated, give dose #1 now, give 2nd dose 4–8wks later, and boost at 12–15m. If infant has had 1 or 2 previous doses, give next dose now, and boost at 12–15m. • For children 12–23m of age: If unvaccinated or only one previous dose before 12m, give 2 doses at least 8wks apart. If 2 doses given before 12m, give booster at least 8wks after previous dose.	**Contraindication** Previous anaphylactic reaction to this vaccine or to any of its components. **Precaution** Moderate or severe acute illness.
Pneumo. polysacch. (PPV) *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 age 10yrs and older who are immunocompromised or have sickle cell disease or functional or anatomic asplenia, give a 2nd PPV at least 3–5yrs after previous PPV.		**Contraindication** Previous anaphylactic reaction to this vaccine or to any of its components. **Precaution** Moderate or severe acute illness.
Hepatitis A *Give IM*	• Give 2 doses at least 6m apart to children who meet the age criteria in the box to the right and who meet any of the following criteria: -Reside in AZ, AK, CA, ID, NV, NM, OK, OR, SD, UT, or WA. Consider vaccination for children living in AR, CO, MO, MT, TX, or WY. -Live in areas with elevated levels of disease (consult local or state health dept.) -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 is MSM adolescent.	• Do not restart series, no matter how long since previous dose. **Note:** Vaqta (Merck) and Havrix (GSK) vaccines were licensed for use in persons 12m and older on 8/11/05 and 10/17/05 respectively. These vaccines were previously licensed for persons 2yrs and older.	**Contraindication** Previous anaphylactic reaction to this vaccine or to any of its components. **Precaution** Moderate or severe acute illness.
Meningococcal Conjugate (MCV4) *Give IM* — Polysaccharide (MPSV4) *Give SC*	• Give 1 dose of MCV4 to adolescents 11–12yrs of age, to adolescents at high school entry (approximately age 15yrs), and to college freshmen living in dormitories. • Vaccinate all children age 2yrs and older who have any of the following risk factors (use MPSV4 if age younger than 11yrs and MCV4 if age 11yrs and older): -Anatomic or functional asplenia, or terminal complement component deficiencies. -Travel to, or reside in countries in which meningococcal disease is hyperendemic or epidemic (e.g., the "meningitis belt" of Sub-Saharan Africa during the dry season [Dec–June]). **Note:** Other adolescents who wish to decrease their risk of meningococcal disease may be vaccinated with MCV4.	If previously vaccinated with MPSV4 and risk continues, give MCV4 5yrs after MPSV4.	**Contraindication** Previous anaphylactic or neurologic reaction to this vaccine or to any of its components, including diphtheria toxoid (for MCV4). **Precaution** Moderate or severe acute illness. **Note:** MCV4 is not licensed for use in children younger than age 11 yrs.

Summary of Recommendations for Adult Immunization

Adapted from the recommendations of the Advisory Committee on Immunization Practices (ACIP)* by the Immunization Action Coalition, August 2005

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*	• Persons age 50yrs and older. • Persons with medical problems (e.g., heart disease, lung disease, diabetes, renal dysfunction, hemoglobinopathy, immunosuppression) and/or people living in chronic-care facilities. • 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) • Persons working or living with at-risk people. • Women who will be pregnant during the influenza season. • All healthcare workers and other persons who provide direct care to at-risk people. • Household contacts and out-of-home caregivers of children ages 0–23m. • 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). • Persons who provide essential community services. • Students or other persons in institutional settings (e.g., dormitory residents). • Anyone wishing to reduce the likelihood of becoming ill with influenza.	• Given every year. • October through November is the *optimal* time to receive annual influenza vaccination to maximize protection; however vaccination may occur in December and throughout the influenza season (typically December through March) or at other times when the risk of influenza exists.	**Contraindication** Previous anaphylactic reaction to this vaccine, to any of its components, or to eggs. **Precaution** Moderate or severe acute illness.
Influenza Live attenuated influenza vaccine (LAIV) *Give intranasally*	• Healthy, non-pregnant persons age 49yrs and younger who meet any of the conditions listed below. - Working or living with at-risk people as listed in the section above. - Healthcare workers or other persons who provide direct care to at-risk people (excluding persons in close contact with severely immunosuppressed persons). - Household contacts and out-of-home caregivers of children ages 0–23m. - Travelers who may be among people from areas of the world where there is current influenza activity (e.g., on organized tours). - Persons who provide essential community services. - Students or other persons in institutional settings (e.g., dormitory residents). - Anyone wishing to reduce the likelihood of becoming ill with influenza.		**Contraindications** • Previous anaphylactic reaction to this vaccine, to any of its components, or to eggs. • 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 receiving immunosuppressive therapy; history of Guillain-Barré syndrome. **Precaution** Moderate or severe acute illness.
Pneumococcal poly-saccharide (PPV23) *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 leak, as well as people living in special environments or social settings (including Alaska Natives and certain American Indian populations). Those at highest risk of fatal pneumococcal infection are persons with anatomic asplenia, functional asplenia, or sickle cell disease; immunocompromised persons including those with HIV infection, leukemia, lymphoma, Hodgkin's disease, multiple myeloma, generalized malignancy, chronic renal failure, or nephrotic syndrome; persons receiving immunosuppressive chemotherapy (including corticosteroids); and those who received an organ or bone marrow transplant and candidates for or recipients of cochlear implants.	• Routinely given as a one-time dose; administer if previous vaccination history is unknown. • One-time revaccination is recommended 5yrs later for persons at highest risk of fatal pneumococcal infection or rapid antibody loss (e.g., renal disease) and for persons age 65yrs and older if the 1st dose was given prior to age 65 and 5yrs or more have elapsed since the previous dose.	**Contraindication** Previous anaphylactic reaction to this vaccine or to any of its components. **Precaution** Moderate or severe acute illness. **Note:** Pregnancy and breastfeeding are not contraindications to the use of this vaccine.

*For specific ACIP recommendations, refer to the official ACIP statements published in *MMWR*. To obtain copies of these statements, call the CDC INFO Contact Center at (800) 232-4636; visit CDC's website at www.cdc.gov/nip/publications/ACIP-list.htm, or visit the Immunization Action Coalition (IAC) website at www.immunize.org/acip.

This table is revised yearly. Visit IAC's website at www.immunize.org/adultrules to make sure you have the most current version. IAC thanks William Atkinson, MD, MPH, from CDC's National Immunization Program, and Linda Moyer, RN, from CDC's Division of Viral Hepatitis, for their assistance. For more information, contact IAC at 1573 Selby Avenue, St. Paul, MN 55104, (651) 647-9009, or email 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 (Hep B) *Give IM* Brands may be used interchangeably.	• All adolescents. • High-risk persons, including household contacts and sex partners of HBsAg-positive persons; injecting drug users; heterosexuals with more than one sex partner in 6 months; men who have sex with men; persons with recently diagnosed STDs; patients receiving hemodialysis and patients with renal disease that may result in dialysis; recipients of certain blood products; healthcare workers 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. When HBsAg-positive persons are identified, offer appropriate disease management. In addition, screen their sex partners and household members, and give the first dose of vaccine at the same visit. If found susceptible, complete the vaccine series.	• Three doses are needed on a 0, 1, 6m schedule. • Alternative timing options for vaccination include 0, 2, 4m and 0, 1, 4m. • There must be 4wks between doses #1 and #2, and 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.	**Contraindication** Previous anaphylactic reaction to this vaccine or to any of its components. **Precaution** Moderate or severe acute illness. **Note:** Pregnancy and breastfeeding are not contraindications to the use of this vaccine.
Hepatitis A (Hep A) *Give IM* Brands may be used interchangeably.	• Persons who travel or work anywhere except the U.S., Western Europe, New Zealand, Australia, Canada, and Japan. • Persons with chronic liver disease, including persons with hepatitis B and C; illegal drug users; men who have sex with men; people with clotting-factor disorders; persons who work with hepatitis A virus in experimental lab settings (not routine medical laboratories); and food handlers when health authorities or private employers determine vaccination to be cost effective. • Anyone wishing to obtain immunity to hepatitis A. **Note:** Prevaccination testing is likely to be cost effective for persons older than age 40yrs, as well as for younger persons in certain groups with a high prevalence of hepatitis A virus infection.	For Twinrix™ (hepatitis A and B combination vaccine [GSK]), three doses are needed on a 0, 1, 6m schedule. Recipients must be age 18yrs or older. • Two doses are needed. • The minimum interval between dose #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. **Note:** Breastfeeding is not a contraindication to the use of this vaccine.
Td (Tetanus, diphtheria) *Give IM* Note: As of 8/24/05, ACIP has not issued recommendations for the use of acellular pertussis combination vaccines (Tdap). See note in next column.	• All adolescents and adults. • After the primary series has been completed, a booster dose is recommended every 10yrs. Make sure your patients have received a primary series of 3 doses. • A booster dose for wound management may be needed as early as 5yrs after receiving a previous dose, so consult ACIP recommendations.* • Use Td, not tetanus toxoid (TT), for all indications. **Note:** Two Tdap products, Boostrix (GSK) and Adacel (sanofi pasteur), were licensed by the FDA in 2005 for use in adults and/or adolescents. Consult package inserts for more information. It is anticipated that ACIP will issue recommendations for these products in late 2005.	• Give booster dose every 10yrs after the primary series has been completed. • For those who are unvaccinated or behind, complete the primary series (spaced at 0, 1–2m, 6–12m intervals). Don't restart the series, no matter how long since the previous dose.	**Contraindication** Previous anaphylactic or neurologic reaction to this vaccine or to any of its components. **Precautions** • Moderate or severe acute illness. • Guillain-Barré syndrome within 6wks of receiving a previous dose of tetanus toxoid-containing vaccine. **Note:** Pregnancy and breastfeeding are not contraindications to the use of this vaccine.
Polio (IPV) *Give IM or SC*	Not routinely recommended for persons 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. Previously vaccinated adults can receive one 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. **Note:** Breastfeeding is not a contraindication to the use of this vaccine.

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 susceptible adults and adolescents should be vaccinated. It is especially important to ensure varicella immunity among household contacts of immunosuppressed persons and among healthcare workers. **Note:** At its June 2005 meeting, ACIP voted to regard birth in the U.S. in 1965 or earlier as presumptive evidence of varicella immunity, with or without a history of having had chickenpox. Persons born in 1966–1997 with a reliable history of chickenpox (such as self or parental report of disease) can be assumed to be immune. For persons who have no reliable history, serologic testing may be cost effective, since most persons with a negative or uncertain history of varicella are immune.	• Two doses are needed. • Dose #2 is given 4–8wks after dose #1. • If varicella vaccine and MMR are both needed and are not administered on the same day, space them at least 4wks apart. • If the second dose is delayed, do not repeat dose #1. Just give dose #2.	**Contraindications** • Previous anaphylactic reaction to this vaccine or to any of its components. • Pregnancy or possibility of pregnancy within 4wks (use contraception). • Persons immunocompromised because of malignancies and primary or acquired cellular immunodeficiency including HIV/AIDS. (See *MMWR* 1999, Vol. 48, No. RR-6.) **Note:** For those on high-dose immunosuppressive therapy, consult ACIP recommendations regarding delay time.* **Precautions** • 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. • Moderate or severe acute illness. **Note:** Breastfeeding is not a contraindication to the use of this vaccine.
Meningococcal Conjugate vaccine (MCV4) *Give IM* — Polysaccharide vaccine (MPSV4) *Give SC*	• College freshmen living in dormitories. • Adolescents and adults with anatomic or functional asplenia or with terminal complement component deficiencies. • 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 during the dry season [Dec–June]). • Microbiologists who are routinely exposed to isolates of *N. meningitidis*. • Military recruits.	• MCV4 is preferred over MPSV4 for persons age 55 yrs and younger, although MPSV4 is an acceptable alternative. • Give one dose to persons with risk factors; revaccinate after 5yrs if risk of disease continues and previous vaccine was MPSV4.	**Contraindication** Previous anaphylactic or neurologic reaction to this vaccine or to any of its components, including diphtheria toxoid (for MCV4). **Precaution** Moderate or severe acute illness. **Note:** Pregnancy and breastfeeding are not contraindications to the use of either vaccine.
MMR (Measles, mumps, rubella) *Give SC*	• Persons born in 1957 or later (including those born outside the U.S.) should receive at least one 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 workers, students entering college and other post–high school educational institutions, and international travelers, should receive a total of two doses. • Persons born before 1957 are usually considered immune, but proof of immunity may be desirable for healthcare workers. • Women of childbearing age (i.e., adolescent girls and premenopausal adult women) who do not have acceptable evidence of rubella immunity or vaccination. • Special attention should be given to immunizing women born outside the U.S. in 1957 or later.	• One or two doses are needed. • If dose #2 is recommended, give it no sooner than 4wks after dose #1. • If varicella vaccine and MMR are both needed and are not administered on the same day, space them at least 4wks apart. • If a pregnant woman is found to be rubella susceptible, administer MMR postpartum.	**Contraindications** • Previous anaphylactic reaction to this vaccine or to any of its components. • Pregnancy or possibility of pregnancy within 4wks (use contraception). • Persons immunocompromised because of cancer, leukemia, lymphoma, immunosuppressive drug therapy, including high-dose steroids or radiation therapy. **Note:** HIV positivity is NOT a contraindication to MMR except for those who are severely immunocompromised. **Precautions** • 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. • Moderate or severe acute illness. • History of thrombocytopenia or thrombocytopenic purpura. **Note:** Breastfeeding is not a contraindication to the use of this vaccine. **Note:** MMR is not contraindicated if a tuberculin skin test (i.e., PPD) was recently applied. If PPD and MMR not given on same day, delay PPD for 4–6wks after MMR.

Suggested intervals between administration of immune globulin preparations for different indications and measles-containing vaccine and varicella vaccine*

Product/Indication	Dose, including mg immunoglobulin G (IgG)/kg body weight†	Suggested Interval before Measles or Varicella Vaccination
RSV monoclonal antibody (Synagis™)§	15 mg/kg intramuscularly (IM)	None
Tetanus (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	0.06 mL/kg (10 mg IgG/kg) IM	3 months
Rabies IG	20 IU/kg (22 mg IgG/kg) IM	4 months
Varicella IG	125 units/10kg (20-40 mg IgG/kg) IM (maximum 625 units)	5 months
Measles prophylaxis IG		
Standard (i.e., nonimmunocompromised contact)	0.25 mL/kg (40 mg IgG/kg) IM	5 months
Immunocompromised contact	0.50 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%)†	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
Respiratory syncytial virus prophylaxis IGIV	750 mg/kg	9 months
IGIV		
Replacement therapy for immune deficiencies¶	300-400 mg/kg IV¶	8 months
Immune thrombocytopenic purpura	400 mg/kg IV	8 months
Immune thrombocytopenic purpura	1000 mg/kg IV	10 months
Kawasaki disease	2 grams/kg IV	11 months

*This table is not intended for determining the correct indications and dosage for using immune globulin products. Unvaccinated persons might not be fully protected against measles during the entire recommended interval, and additional doses of immune globulin and/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 might vary also. 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.
(**Source:** Mason W, Takahashi M, Schneider T. Persisting passively acquired measles antibody following gamma globulin therapy for Kawasaki disease and response to live virus vaccination [Abstract 311]. Presented at the 32nd meeting of the Interscience Conference on Antimicrobial Agents and Chemotherapy, Los Angeles, California, October, 1992.)

§Contains antibody only to respiratory syncytial virus (RSV)

†Assumes a serum IgG concentration of 16 mg/mL.

¶Measles and varicella vaccination is recommended for children with asymptomatic or mildly symptomatic human immunodeficiency virus (HIV) infection but is contraindicated for persons with severe immunosuppression from HIV or any other immunosuppressive disorder.

From ACIP "General Recommendations on Immunization" February 8, 2002

Healthcare Worker 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 IM or intranasally, respectively.
MMR	For persons born in 1957 or later without serologic evidence of immunity or prior vaccination, give 2 doses of MMR, 4 weeks apart. Give SC.
Varicella (chickenpox)	For persons 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	All adults need a Td booster dose every 10 years, following the completion of the primary 3-dose series. Give IM. **Note:** As of Aug. 2005, CDC's Advisory Committee on Immunization Practices (ACIP) is in discussion about the use of acellular pertussis vaccine in healthcare workers (HCWs).
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 HCWs who may have on-the-job exposure to fecal material.

Hepatitis B

Healthcare workers (HCWs) 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 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: Persons 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.* It is also possible that non-responders are persons who are HBsAg positive. Testing should be considered. Persons found to be HBsAg positive should be counseled and medically evaluated.

Note: Anti-HBs testing is not recommended routinely for previously vaccinated HCWs who were not tested 1–2 months after their original vaccine series. These HCWs should be tested for anti-HBs when they have an exposure to blood or body fluids. If found to be anti-HBs negative, the HCW should be protected.*

Influenza

Trivalent (Inactivated) Influenza Vaccine (TIV): May give to any HCW.

Live, Attenuated Influenza Vaccine (LAIV): May give to any non-pregnant healthy HCW age 49 years and younger.

1. All HCWs 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 HCWs 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)

Persons who work in medical facilities should be immune to measles and rubella. Immunity to mumps is highly desirable.

- 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" 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 vaccine separated by 28 days or more, 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, healthcare facilities should consider recommending a dose of MMR vaccine to unvaccinated HCWs born before 1957 who are in either of the following categories: (a) do not have a history of measles disease or laboratory evidence of measles immunity and (b) do not have laboratory evidence of rubella immunity.

Varicella

It is recommended that all HCWs be immune to varicella, either from a reliable history of varicella disease or vaccination. Serologic screening for varicella immunity need not be done before vaccinating unless the healthcare institution considers it cost effective. Routine postvaccination testing of HCWs for antibodies to varicella is not recommended because commercial tests are often not sensitive enough to measure vaccine-induced immunity.

Tetanus/Diphtheria (Td)

All persons should receive a Td booster every 10 years. A 3-dose primary series of a tetanus/diphtheria-containing product (DTP, DTaP, DT, Td) is necessary before a booster dose is given. **Note:** As of Aug. 2005, ACIP is in discussion about the use of acellular pertussis vaccine in HCWs.

Meningococcal

Vaccination is recommended for microbiologists who are routinely exposed to isolates of *N. meningitidis.* Use of MCV4 is preferred among persons ages 11–55 years; give IM. If MCV4 is unavailable, MPSV4 is an acceptable alternative for persons ages 11–55 years. Use of MPSV4 is recommended for persons older than age 55; give SC.

References

*Table 3: "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/nip/publications/ACIP-list.htm; or visit the Immunization Action Coalition (IAC) website at www.immunize.org/acip.

Adapted with thanks from the Michigan Department of Community Health

www.immunize.org/catg.d/p2017.pdf • Item #P2017 (9/05)

Vaccination of Persons with Primary and Secondary Immune Deficiencies

PRIMARY				
Category	**Specific Immunodeficiency**	**Contraindicated Vaccines***	**Recommended Vaccines**	**Effectiveness & Comments**
B-lymphocyte (humoral)	Severe antibody deficiencies (e.g., X-linked agammaglobulinemia and common variable immunodeficiency)	OPV[1] Smallpox LAIV BCG Ty21a (live 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; 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[1] Other live vaccines appear to be safe, but caution is urged.	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 [2,3]	Pneumococcal Influenza (TIV)	Vaccines may be ineffective.
	Partial defects (e.g., most patients with DiGeorge syndrome, Wiskott-Aldrich syndrome, ataxia-telangiectasia)	All live vaccines [2,3]	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, C2, C3, 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[2]	Pneumococcal[4] Influenza (TIV) (to decrease secondary bacterial infection).	All inactivated vaccines safe and probably effective. Live viral vaccines probably safe and effective.

*Any vaccine that is not specifically contraindicated may be used if otherwise indicated.

[1] OPV is no longer recommended for routine use in the United States.
[2] Live bacterial vaccines: BCG, and Ty21a *Salmonella typhi* vaccine.
[3] Live viral vaccines: MMR, OPV, LAIV, yellow fever, varicella, and vaccinia (smallpox). Smallpox vaccine is not recommended for children.
[4] 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***	**Recommended Vaccines**	**Effectiveness & Comments**
HIV/AIDS	OPV[1] Smallpox BCG LAIV Withhold MMR and varicella in severely immunocompromised children.	Influenza (TIV) Pneumococcal Consider Hib (if not administered in infancy) and Mengingococcal vaccination.	MMR, varicella, and all inactivated vaccines, including inactivated influenza, may be effective.[4]
Malignant neoplasm, transplantation, immunosuppressive or radiation therapy	Live viral and bacterial, depending on immune status.[2,3]	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)	All routine vaccines probably effective.

*Any vaccine that is not specifically contraindicated may be used if otherwise indicated.

[1] OPV is no longer recommended for routine use in the United States.
[2] Live bacterial vaccines: BCG and Ty21a *Salmonella typhi* vaccine.
[3] Live viral vaccines: MMR, OPV, LAIV, yellow fever, varicella, and vaccinia (smallpox). Smallpox vaccine is not recommended for children.
[4] HIV-infected children should receive IG after exposure to measles, and may receive varicella and measles vaccine if CD4+ lymphocyte count is ≥15%.

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, ed. *Red Book: 2003 Report of the Committee on Infectious Diseases*. 26th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2003: [71-72] and Centers for Disease Control and Prevention. Recommendations of the Advisory Committee on Immunization Practices (ACIP): Use of Vaccines and Immune Globulins in Persons with Altered Immunocompetence. *MMWR* 1993: 42 (No. RR-4): [1-18].

APPENDIX B
Vaccines

Appendix B

U.S. Vaccines

Vaccine	Name	Manufacturer	Type	Route	Comments
Anthrax	BioThrax	BioPort	Inactivated Bacterial	SC	
DTaP	Daptacel	sanofi	Inactivated Bacterial	IM	Toxoids (tetanus & diphtheria) + Vaccine (pertussis). Not licensed for 5th dose.
	Infanrix	GlaxoSmithKline	Inactivated Bacterial	IM	Toxoids (tetanus & diphtheria) + Vaccine (pertussis).
	Tripedia	sanofi	Inactivated Bacterial	IM	Toxoids (tetanus & diphtheria) + Vaccine (pertussis).
DT	(Generic)	sanofi	Inactivated Bacterial Toxoids	IM	Pediatric formulation
DTaP/Hib	TriHIBit	sanofi	Inactivated Bacterial	IM	ActHIB reconstituted with Tripedia. Licensed for 4th dose of DTaP & Hib series (not primary series).
DTaP/IPV/HepB	Pediarix	GlaxoSmithKline	Inactivated Bacterial & Viral	IM	Approved for doses at 2, 4, 6 months (through 6 years of age). Not licensed for boosters.
Haemophilus influenzae type b (Hib)	HibTITER	Wyeth	Inactivated Bacterial	IM	**HbOC**. Polysaccharide conjugate (diphtheria protein carrier). 4-dose schedule.
	PedvaxHIB	Merck	Inactivated Bacterial	IM	**PRP-OMP**. Polysaccharide conjugate (mening. protein carrier). 3-dose schedule.
	ActHIB	sanofi	Inactivated Bacterial	IM	**PRP-T**. Polysaccharide conjugate (tetanus toxoid carrier). 4-dose schedule.
Hepatitis A	Havrix	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	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	GlaxoSmithKline	Inactivated Viral (recombinant)	IM	Pediatric (≤19) and adult formulations. Pediatric formulation is not licensed for adults.
	Recombivax HB	Merck	Inactivated Viral (recombinant)	IM	Pediatric (≤19), adult, and dialysis formulations. Two pediatric doses may be substituted for an adult dose.

Appendix B

Vaccine	Name	Manufacturer	Type	Route	Comments
HepA/HepB	Twinrix	GlaxoSmithKline	Inactivated Viral	IM	Pediatric dose of HepA + adult dose of HepB. Minimum age = 18 years.
HepB/Hib	Comvax	Merck	Inactivated Bacterial & Viral	IM	Should not be used for HepB birth dose.
Influenza	Fluarix	GlaxoSmithKline	Inactivated Viral	IM	Trivalent Types A & B. Minimum age = 18 years.
	Fluvirin	Chiron	Inactivated Viral	IM	Trivalent Types A & B Purified surface antigen. Minimum age = 4 years.
	Fluzone	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.
	FluMist	Medimmune	Live attenuated viral	Intra-nasal	Trivalent Types A & B. Age range 5-49 years.
Japanese Encephalitis	JE-Vax	sanofi	Inactivated viral	SC	
MMR	M-M-R II	Merck	Live attenuated viral	SC	Measles, mumps, rubella.
MMRV	ProQuad	Merck	Live attenuated viral	SC	Measles, mumps, rubella, varicella.
Measles	Attenuvax	Merck	Live attenuated viral	SC	Edmonston-Enders strain
Mumps	Mumpsvax	Merck	Live attenuated viral	SC	Jeryl Lynn strain
Rubella	Meruvax II	Merck	Live attenuated viral	SC	RA 27/3 strain
Meningococcal	Menomume	sanofi	Inactivated bacterial	SC	Polysaccharide, containing serogroups A, C, Y, & W-135.
	Menactra	sanofi	Inactivated bacterial	IM	Polysaccharide conjugate (diphtheria toxoid carrier), containing serogroups A, C, Y, & W-135. Age range 11-49.
Pneumococcal	Pneumovax 23	sanofi	Inactivated bacterial	SC or IM	Polysaccharide. Contains 23 strains.
	Prevnar	Wyeth	Inactivated bacterial	IM	Polysaccharide conjugate (diphtheria protein carrier). Contains 7 strains.
Polio	Ipol	sanofi	Inactivated viral	SC or IM	Trivalent, Types 1, 2, & 3.
Rabies	BioRab	BioPort	Inactivated viral	IM	
	Imovax Rabies	sanofi	Inactivated viral	IM	
	RabAvert	Chiron	Inactivated viral	IM	

Vaccine	Name	Manufacturer	Type	Route	Comments
Td	Decavac	sanofi	Inactivated bacterial toxoids	IM	Tetanus/diphtheria toxoids. Adult formulation
	(Generic)	Massachusetts Biological Labs	Inactivated bacterial toxoids	IM	Tetanus/diphtheria toxoids. Adult formulation
Tdap	Boostrix	GlaxoSmithKline	Inactivated bacterial	IM	Tetanus & diphtheria toxoids & pertussis vaccine. Licensed for ages 10-18.
	Adacel	sanofi	Inactivated bacterial	IM	Tetanus & diphtheria toxoids & pertussis vaccine. Licensed for ages 11-64.
TT	(Generic)	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	Merck	Live viral	SC	
Vaccinia (Smallpox)	Dryvax	Wyeth	Live viral	Percu-taneous	
Yellow Fever	YF-Vax	sanofi	Live viral	SC	

November 2005

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*		
Excipient	Use	Vaccine
Albumin, egg (Ovalbumin)	Growth medium	Rabies (*RabAvert*)
Albumin, human serum	Component of growth medium, protein stabilizer	Measles (*Attenuvax*), MMR (*MMR-II*), 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*), Mumps (*Mumpsvax*), Rabies (*Imovax, RabAvert*), Rubella (*Meruvax II*), Vaccinia (*Dryvax*), Varicella (*Varivax*)
Aluminum hydroxide	Adjuvant	Anthrax (*BioThrax*), DTaP (*Infanrix*), DTaP-Hep B-IPV (*Pediarix*), DT (Massachusetts), Td (Massachusetts), Hepatitis A (*Havrix*), Hepatitis A-Hepatitis B (*Twinrix*), Hepatitis B (*Engerix-B*), Tdap (*Boostrix*)
Aluminum phosphate	Adjuvant	DTaP (*Daptacel*), Td (Aventis Pasteur, Massachusetts), Hepatitis A-Hepatitis B (*Twinrix*), Pneumococcal (*Prevnar*), Rabies (*BioRab*)
Aluminum potassium sulfate	Adjuvant	DTaP (*Daptacel, Tripedia*), DTaP-Hib (*TriHIBit*), DT (Aventis Pasteur)
Amino acids	Component of growth medium	Anthrax (*BioThrax*), Hepatitis A (*Havrix*), Hepatitis A-Hepatitis B (*Twinrix*), Td (Aventis Pasteur), Typhoid oral (*Vivotif*)
Ammonium sulfate	Protein fractionation	DTaP-Hib (*TriHIBit*), Hib (*ActHIB*)
Amphotericin B	Antibacterial	Rabies (*RabAvert*)
Ascorbic acid	Antioxidant	Typhoid oral (*Vivotif*)
Bactopeptone	Component of growth medium	Influenza (varies seasonally)

Vaccine Excipient & Media Summary

Excipients Included in US Licensed Vaccines*		
Excipient	Use	Vaccine
Beta-propiolactone	Viral inactivator	Influenza (*Fluvirin*), Rabies (*Imovax*, *RabAvert*)
Benzethonium chloride	Preservative	Anthrax (*BioThrax*)
Brilliant green	Dye	Vaccinia (*Dryvax-historic*)
Chlortetracycline	Antibacterial	Rabies (*RabAvert*), Vaccinia (*Dryvax*)
DNA	Manufacturing residue	Hepatitis A (*Vaqta*)
Ethylenediamine-tetraacetic acid sodium (EDTA)	Preservative	Rabies (*RabAvert*), Varicella (*Varivax*)
Egg protein	Manufacturing residue	Influenza (all brands), Yellow fever (*YF-Vax*)
Formaldehyde, formalin	Antimicrobial, preservative	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*), Japanese encephalitis (*JE-Vax*), Poliovirus inactivated (*Ipol*), Tdap (*Boostrix*)
Gelatin	Stabilizer in freeze-drying, solvent	DTaP (*Tripedia*), DTaP-Hib (*TriHIBit*), Influenza (*Fluzone*), Japanese encephalitis (*JE-Vax*), Measles (*Attenuvax*), Mumps (*Mumpsvax*), Rubella (*Meruvax II*), MMR (*MMR-II*), Rabies (*RabAvert*), Typhoid oral (*Vivotif*), Varicella (*Varivax*), Yellow fever (*YF-Vax*)
Gentamicin	Antibacterial	Influenza (*FluMist*)
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)
Hydrochloric acid	Adjust pH	DTaP (most brands), DT (most brands)
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*)
Monosodium glutamate	Stabilizer	Influenza (*FluMist*), Varicella (*Varivax*)
Mouse serum protein	Manufacturing residue	Japanese encephalitis (*JE-Vax*)

Vaccine Excipient & Media Summary

Excipients Included in US Licensed Vaccines*		
Excipient	Use	Vaccine
MRC-5 cellular protein	Manufacturing residue	Hepatitis A (*Havrix, Vaqta*), Hepatitis A-Hepatitis B (*Twinrix*), 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*), Poliovirus inactivated (*Ipol*), Rabies (*Imovax, RabAvert*), Vaccinia (*DryVax*), Varicella (*Varivax*)
Phenol	Preservative, antibacterial	Pneumococcal (*Pneumovax-23*), Typhoid inactivated (*Typhim Vi*) Vaccinia (*Dryvax*)
Phenol red (phenolsulfonphthalein)	pH indicator, dye	Rabies (*Imovax*)
2-Phenoxyethanol	Preservative	DTaP (*Infanrix, Daptacel*), DTaP-Heb B-IPV (*Pediarix*), Hepatitis A (*Havrix*), Hepatitis A-Hepatitis B (*Twinrix*), Poliovirus inactivated (*Ipol*), Td (Aventis 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 (*FluMist*), Measles (*Attenuvax*), Meningococcal (*Menactra*), Mumps (*Mumpsvax*), Poliovirus inactivated (*Ipol*), Rabies (*BioRab*), Rubella (*Meruvax II*), MMR (*MMR-II*), Typhoid inactivated (*Typhim Vi*), Varicella (*Varivax*)
Polydimethylsilozone	Antifoaming agent	Typhoid inactivated (*Typhim Vi*)
Polyethylene glycol p-isooctylphenyl ether (Triton X-100)	Nonionic surfactant (viral inactivation)	Influenza (*Fluzone*)
Polymyxin B	Antibacterial	DTaP-Heb B-IPV (*Pediarix*), Influenza (*Fluvirin*), Poliovirus inactivated (*Ipol*), Vaccinia (*Dryvax*)
Polyoxyethylene9-10 nonyl phenol (Triton N-101, octoxynol 9)	Nonionic surfactant (viral inactivation)	Influenza (*Fluvirin*)
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*), Tdap (*Boostrix*)
Potassium glutamate	Stabilizer	Rabies (*RabAvert*)

Vaccine Excipient & Media Summary

Excipients Included in US Licensed Vaccines*		
Excipient	Use	Vaccine
Sodium acetate	Adjust pH	DT (some brands), Td (some brands)
Sodium borate	Adjust pH	Hepatitis A (*Vaqta*), Hib-Hepatitis B (*Comvax*)
Sodium chloride	Adjust tonicity	Most vaccines, including Anthrax, BCG, Measles, Meningococcal (*Menactra*), Mumps, MMR, Pneumococcal, Polio inactivated, Rabies, Rubella, Typhoid inactivated, Varicella, Yellow fever, Tdap (*Boostrix*)
Sodium hydroxide	Adjust pH	DT (most brands), Td (most brands)
Sorbitol	Stabilizer, solvent	Measles (*Attenuvax*), Mumps (*Mumpsvax*), Rubella (*Meruvax II*), MMR (*MMR-II*), Yellow fever (*YF-Vax*)
Streptomycin	Antibacterial	Poliovirus inactivated (*Ipol*), Vaccinia (*Dryvax*)
Sucrose	Stabilizer	DTaP-Hib (*TriHIBit*), Hib (*Act-HIB*), Influenza (*FluMist*), Measles (*Attenuvax*), Mumps (*Mumpsvax*), MMR (*MMR-II*), Typhoid oral (*Vivotif*), Varicella (*Varivax*)
Thimerosal	Preservative in some multi-dose containers (see package labeling for precise content)	DTaP (some multidose containers), DTaP-Hib (*TriHIBit*), DT (some multidose containers), Td (some multidose containers), Hepatitis B (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.
Urea	Stabilizer	Varicella vaccine (*Varivax*, refrigerator stable)
Vitamins unspecified	Component of growth medium	Anthrax (*BioThrax*), Rabies (*Imovax*), Td (Aventis Pasteur)
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*)

* Proprietary names appear in italics.

Vaccine Excipient & Media Summary

Vaccine-Production Media*	
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, 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*), Poliovirus inactivated (*Poliovax*), Rabies (*Imovax*), Varicella (*Varivax*)
Human diploid tissue culture, WI-38	Rubella (*Meruvax II*), combination vaccines containing it, Varicella (*Varivax*)
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*)
Monkey kidney tissue culture, Vero (Vervet or African green monkeys)	DTaP-Hep B-IPV (poliovirus component, *Pediarix*), Poliovirus inactivated (*Ipol*)
Mouse brain	Japanese encephalitis (*JE-Vax*)
Mueller-Hinton agar medium	Meningococcal conjugate (*Menactra*)
Mueller-Miller medium	Diphtheria and tetanus vaccines (most brands), meningococcal conjugate (*Menactra*)
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*), Hib-Hepatitis B (*Comvax*), Medium for growing *Corynebacterium diphtheriae* strain C7 (b197) to obtain CRM_{197} protein for conjugation to polysaccharides (*HibTiter*, *Prevnar*).

* Proprietary names appear in italics.

Vaccine Excipient & Media Summary

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Vaccine Excipient & Media Summary, Part 2

Excipients Included in U.S. Vaccines, by Vaccine

Vaccine	Contains
Anthrax (BioThrax)	Aluminum Hydroxide, Amino Acids, Benzethonium Chloride, Formaldehyde or Formalin, Sodium Chloride, Vitamins (unspecified)
BCG (Tice)	Lactose, Sodium Chloride
DTaP (DAPTACEL)	Aluminum Phosphate, Aluminum Potassium Sulfate, Formaldehyde or Formalin, 2-Phenoxyethanol
DTaP (Infanrix)	Aluminum Hydroxide, Formaldehyde or Formalin, Glutaraldhyde, 2-Phenoxyethanol, Polysorbate 80
DTaP (Tripedia)	Aluminum Potassium Sulfate, Formaldehyde or Formalin, Gelatin, Polysorbate 80, Thimerosal*
DTaP (Most brands)	Hydroehloric Acid, Phosphate Buffers (e.g., disodium, monosodium, potassium, sodium dihydrogen phosphate)
DTaP/Hib (TriHIBit)	Aluminum Potassium Sulfate, Ammonium Sulfate, Formaldehyde or Formalin, Gelatin, Polysorbate 80, Sucrose, Thimerosal*
DTaP/HepB/IPV (Pediarix)	Aluminum Hydroxide, Formaldehyde or Formalin, Glutaraldhyde, Neomycin, 2-Phenoxyethanol, Polymyxin B, Polysorbate 80, Thimerosal*, Yeast Protein
DT (Aventis)	Aluminum Potassium Sulfate, Formaldehyde or Formalin
DT (Massachusetts)	Aluminum Hydroxide, Formaldehyde or Formalin
DT (Some brands)	Glycine, Hydrochloric Acid, Phosphate Buffers (e.g., disodium, monosodium, potassium, sodium dihydrogen phosphate), Sodium Acetate, Sodium Hydroxide, Thimerosal (some multidose containers)
Hib (ACTHib)	Ammonium Sulfate, Formaldehyde or Formalin, Phosphate Buffers (e.g., disodium, monosodium, potassium, sodium dihydrogen phosphate), Sucrose
Hib (PedvaxHib)	Aluminum Hydroxyphosphate Sulfate, Sodium Chloride
Hib (HibTITER)	Yeast Protein
Hib (Some packages)	Lactose
Hib/Hep B (Comvax)	Formaldehyde or Formalin, Sodium Borate, Yeast Protein
Hep A (Havrix)	Bovine Albumin or Serum, Aluminum Hydroxide, Amino Acids, Formaldehyde or Formalin, MRC-5 Cellular Protein, 2-Phenoxyethanol, Phosphate Buffers (e.g., disodium, monosodium, potassium, sodium dihydrogen phosphate), Polysorbate 20
Hep A (Vaqta)	Bovine Albumin or Serum, DNA, Formaldehyde or Formalin, MRC-5 Cellular Protein, Sodium Borate
Hep B (Engerix-B)	Aluminum Hydroxide, Phosphate Buffers (e.g., disodium, monosodium, potassium, sodium dihydrogen phosphate), Thimerosal*, Yeast Protein

Vaccine	Contains
Hep B (Recombivax)	Yeast Protein
HepA/HepB (Twinrix)	Aluminum Hydroxide, Aluminum Phosphate, Amino Acids, Formaldehyde or Formalin, MRC-5 Cellular Protein, Neomycin, 2-Phenoxyethanol, Phosphate Buffers (e.g., disodium, monosodium, potassium, sodium dihydrogen phosphate), Polysorbate 20, Thimerosal*, Yeast Protein
Influenza (Fluarix)	Egg Albumin (Ovalbumin), Egg Proteiin, Formaldehyde or Formalin, Gentamicin, Hydrocotrisone, Oetoxynol-10, α-Tocopheryl Hydrogen Succinate, Polysorbate 80, Sodium Deoxycholate, Thimerosal*
Influenza (Fluvirin)	Beta-Propiolaetone, Egg Protein, Neomycin, Polymyxin B, Polyoxyethylene 9-10 Nonyl Phenol (Triton N-101, Octoxynol 9), Thimerosal (multidose containers)
Influenza (Fluzone)	Egg Protein, Formaldehyde or Formalin, Gelatin, Polyethylene glycol p-isooctylphenyl ether (Triton X-100), Thimerosal (multidose containers)
Influenza (FluMist)	Egg Protein, Gentamicin, Monosodium Glutamate, Phosphate Buffers (e.g., disodium, monosodium, potassium, sodium dihydrogen phosphate), Suerose
Influenza (varies seasonally)	Bactopeptone
IPV (Ipol)	Formaldehyde or Formalin, Neomycin, 2-Phenoxyethanol, Phosphate Buffers (e.g., disodium, monosodium, potassium, sodium dihydrogen phosphate), Polymyxin B, Sodium Chloride, Streptomycin
Japanese Encephalitis (JE-Vax)	Formaldehyde or Formalin, Gelatin, Mouse Serum Protein, Thimerosal
Measles (Attenuvax)	Human Serum Albumin, Bovine Albumin or Serum, Gelatin, Neomycin, Phosphate Buffers (e.g., disodium, monosodium, potassium, sodium dihydrogen phosphate), Sodium Chloride, Sorbitol, Sucrose
Meningoeoccal (Menactra)	Phosphate Buffers (e.g., disodium, monosodium, potassium, sodium dihydrogen phosphate), Sodium Chloride
Meningocoeeal (Menomune)	Lactose, Thimerosal (10-dose vials only)
Mumps (Mumpsvax)	Human Serum Albumin, Bovine Albumin or Serum, Gelatin, Neomycin, Phosphate Buffers (e.g., disodium, monosodium, potassium, sodium dihydrogen phosphate), Sodium Chloride, Sorbitol, Sucrose
MMR (MMR-II)	Human Serum Albumin, Bovine Albumin or Serum, Gelatin, Neomycin, Phosphate Buffers (e.g., disodium, monosodium, potassium, sodium dihydrogen phosphate), Sodium Chloride, Sorbitol, Sucrose
MMRV (ProQuad)	Sucrose, Gelatin, Sodium Chloride, Sorbitol, Monosodium L-glutamate, Human Serum Albumin, MRC-5 Cellular Protein, Neomycin, Bovine Albumin or Serum, Sodium Phosphate Dibasic, Sodium Bicarbonate, Potassium Phosphate Monobasic, Potassium Chloride, Potassium Phosphate Dibasie
Pneumoeoeeal (Pneumovax)	Phenol, Sodium Chloride
Pneumocoeeal (Prevnar)	Aluminum Phosphate, Sodium Chloride

Vaccine	Contains
Rabies (Biorab)	Aluminum Phosphate, Phosphate Buffers (e.g., disodium, monosodium, potassium, sodium dihydrogen phosphate), Sodium Chloride, Thimerosal
Rabies (Imovax)	Human Serum Albumin, Bovine Albumin or Serum, Beta-Propiolactone,MRC-5 Cellular Protein, Neomycin, Phenol Red (Phenolsulfonphthalein), Sodium Chloride, Vitamins (unspecified)
Rabies (RabAvert)	Egg Albumin (Ovalbumin), Bovine Albumin or Serum, Amphotericin B, Beta-Propiolactone, Chlortetracycline, Ethylenediamine-Tetraacetic Acid Sodium (EDTA), Gelatin, Neomycin, Potassium Glutamate, Sodium Chloride
Rubella (Meruvax II)	Human Serum Albumin, Bovine Albumin or Serum, Gelatin, Neomycin, Phosphate Buffers (e.g., disodium, monosodium, potassium, sodium dihydrogen phosphate), Sodium Chloride, Sorbitol
Td (Decavac)	Aluminum Phosphate, Amino Acids, Formaldehyde or Formalin, 2-Phenoxyethanol, Thimerosal (some multidose containers), Vitamins (unspecified)
Td (Massachusetts)	Aluminum Hydroxide, Aluminum Phosphate, Formaldehyde or Formalin, Thimerosal (some multidose containers)
Td (Some Brands)	Glycine, Sodium Acetate, Sodium Hydroxide
Tdap (Adacel)	Aluminum Phosphate, Formaldehyde or Formalin, Glutaraldehyde, 2-Phenoxyethanol, Sodium Chloride
Tdap (Boostrix)	Aluminum Hydroxide, Formaldehyde or Formalin, Glutaraldehyde, Polysorbate 80
Typhoid (inactivated – Typhim Vi)	Phenol, Phosphate Buffers (e.g., disodium, monosodium, potassium, sodium dihydrogen phosphate), Polydimethylsilozone, Sodium Chloride
Typhoid (oral – TY21a)	Amino Acids, Ascorbic Acid, Gelatin, Lactose, Magnesium Stearate, Sucrose
Vaccinia (DryVax)	Bovine Albumin or Serum, Brilliant Green (historic), Chlortetracycline, Glycerin, Neomycin, Phenol, Polymyxin B, Streptomycin, Urea (refrigerator-stable formulation only)
Varicella (Varivax)	Bovine Albumin or Serum, Ethylenediamine-Tetraacetic Acid Sodium (EDTA), Gelatin, Monosodium Glutamate, MRC-5 Cellular Protein, Neomycin, Phosphate Buffers (e.g., disodium, monosodium, potassium, sodium dihydrogen phosphate), Sodium Chloride, Sucrose
Yellow Fever (YF-Vax)	Egg Protein, Gelatin, Sodium Chloride, Sorbitol

*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 (<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.; 2006 with additional content from individual products' package inserts.

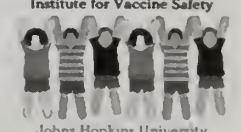
Thimerosal Content in Some US Licensed Vaccines

updated September 13, 2005

Vaccine	Brand Name		Manufacturer	Thimerosal Concentration(1)	Mercury mcg/0.5 ml
Anthrax	Biothrax		BioPort Corp	0	0
DTaP	Tripedia		sanofi pasteur	*	*
	Infanrix		GlaxoSmithKline	0	0
	Daptacel		sanofi pasteur	0	0
DTaP-HepB-IPV	Pediarix		GlaxoSmithKline	*	*
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	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 /OmniHib		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	*	*
	Recombivax HB preservative free		Merck	0	0
Hep A-B	Twinrix		GlaxoSmithKline	*	*
Influenza 2004 /5 Formula	Fluzone	prefilled syringe (0.25 mL)	sanofi pasteur	*	*
		prefilled syringe (0.5mL)		.01%	25
		multi-dose (5 mL)		.01%	25
	Fluvirin preservative free		Evans	*	*
	Fluvirin			.01%	25
	FluMist		MedImmune	0	0
2005-6 Formula	Fluarix		GlaxoSmithKline	*	*
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		*	*
MMR	M-M-R II		Merck	0	0
MMR-Varicella	ProQuad		Merck	0	0
Pneumococcal	Prevnar		Wyeth-Ayerst	0	0
	Pneumovax 23		Merck	0	0
Rabies	RabAvert		Chiron	0	0
	IMOVAX		sanofi pasteur	0	0
Typhoid Fever	Typhim Vi		sanofi pasteur	0	0
	Vivotif		Berna Biotch	0	0
Varicella	Varivax		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 micrograms 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. The trace amounts (<0.3 mcg) of mercury left after post-production thimerosal removal have no biological effect. JAMA 1999;282(18) and JAMA 2000;283(16).



Institute for Vaccine Safety
Johns Hopkins University
www.vaccinesafety.edu

Pediatric/VFC Vaccine Price List – 11/8/05

Vaccine	Brandname/ Tradename	Packaging	CDC Cost/ Dose	Private Sector Cost/ Dose	Contract End Date	Manufacturer
DTaP/	Tripedia® DAPTACEL®	10 pack - 1 dose vials 10 pack - 1 dose vials	$12.25 $12.75	$21.40 $22.04	3/31/06	sanofi pasteur
DTaP/	Infanrix®	10 pack - 1 dose vials 5 pack - 1 dose T-L syringes. No Needle	$12.75 $12.75	$20.96 $21.44	3/31/06	GlaxoSmithKline
DTaP-Hep B-IPV*	Pediarix®	10 pack - 1 dose vials 5 pack - 1 dose T-L syringes. No Needle	$38.34 $38.34	$70.72 $70.72	3/31/06	GlaxoSmithKline
DTaP-Hib #	TriHIBit®	5 pack - 1 dose vials	$24.62	$41.72	3/31/06	sanofi pasteur
e-IPV•	IPOL®	10 dose vials	$10.42	$21.80	3/31/06	sanofi pasteur
Hepatitis B-Hib^	COMVAX®	10 pack - 1 dose vials	$24.50	$43.56	3/31/06	Merck
Hepatitis A Pediatric•	VAQTA®	10 pack - 1 dose vials	$12.15	$30.37	3/31/06	Merck
Hepatitis A Pediatric•	Havrix®	1 dose vials 10 pack - 1 dose vials 5 pack - 1 dose T-L syringes. No Needle	$12.10 $12.10 $12.10	$28.63 $27.41 $27.41	3/31/06	GlaxoSmithKline
Hepatitis A-Hepatitis B 18 only^	Twinrix®	10 pack - 1 dose vials 5 pack - 1 dose T-L syringes, No Needle	$36.91 $36.91	$78.16 $78.42	3/31/06	GlaxoSmithKline
Hepatitis B• Pediatric/Adolescent	ENGERIX B®	1 dose vials 10 pack - 1 dose vials 5 pack - 1 dose T-L syringes, No Needle	$9.00 $9.00 $9.00	$21.37 $21.37 $21.37	3/31/06	GlaxoSmithKline
Hepatitis B• Pediatric/Adolescent	RECOMBIVAX HB®	10 pack - 1 dose vials	$9.00	$23.20	3/31/06	Merck
Hepatitis B 2 dose• Adolescent (11-15)	RECOMBIVAX HB®	10 pack - 1 dose vials	$24.25	$59.09	3/31/06	Merck
Hib•	PedvaxHIB®	10 pack - 1 dose vials	$10.22	$22.77	3/31/06	Merck
Hib•	ActHIB®	5 pack - 1 dose vials	$7.664	$22.53	3/31/06	sanofi pasteur
Hib•	HibTITER®	5 pack - 1 dose vials	$7.86	$22.86	3/31/06	Wyeth Vaccines
Meningococcal Conjugate (Groups A, C, Y and W-135)	Menactra™	1 dose vials 5 pack - 1 dose vials	$68.00 $68.00	$82.00 $82.00	3/31/06	sanofi pasteur
MMR/	MMRII®	10 pack - 1 dose vials	$16.67	$40.37	3/31/06	Merck
Pneumococcal 7-valent• (Pediatric)	Prevnar®	5 pack - 1 dose vials	$54.12	$65.95	3/31/06	Wyeth/Lederle
Tetanus & Diphtheria Toxoids^	DECAVAC™	10 pack – 1 dose syringes No Needle	$15.90	$17.50	3/31/06	sanofi pasteur

Vaccine	Brandname/ Tradename	Packaging	CDC Cost/ Dose	Private Sector Cost/ Dose	Contract End Date	Manufacturer
Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis/	BOOSTRIX	10 pack - 1 dose vials 5 pack - 1 dose TL syringes, No Needle	$28.75 $28.75	$35.25 $35.25	3/31/06	GlaxoSmithKline
Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis/	ADACEL	10 pack - 1 dose vials	$30.75	$35.75	3/31/06	sanofi pasteur
Varicella•	Varivax®	10 pack - 1 dose vials	$52.25	$66.81	3/31/06	Merck

/ Vaccine cost includes $2.25 dose Federal Excise Tax
Vaccine cost includes $3.00 per dose Federal Excise Tax
^ Vaccine cost includes $1.50 per dose Federal Excise Tax
* Vaccine cost includes $3.75 per dose Federal Excise Tax
• Vaccine cost includes $0.75 per dose Federal Excise Tax
¤ Vaccines which contain Thimerosal as a preservative

Find current Vaccine Price Lists online at
www.cdc.gov/nip/vfc/cdc_vac_price_list.htm

Adult Vaccine Price List – 11/8/05

Vaccine	Brandname/ Tradename	Packaging	CDC Cost/ Dose	Private Sector Cost/ Dose	Contract End Date	Manufacturer
Hepatitis A Adult•	VAQTA®	1 dose vials 10 pack - 1 dose vials	$18.50 $18.50	$63.51 $59.99	6/30/06	Merck
Hepatitis A Adult•	Havrix®	1 dose vials 5 pack - 1 dose T-L syringes, No Needle	$18.50 $18.50	$56.17 $54.98	6/30/06	GlaxoSmithKline
Hepatitis A-Hepatitis B Adult^	Twinrix®	10 pack - 1 dose vials 5 pack - 1 dose T-L syringes, No Needle	$36.91 $36.91	$78.16 $78.42	6/30/06	GlaxoSmithKline
Hepatitis B-Adult•	RECOMBIVAX HB®	1 dose vials 10 pack - 1 dose vials	$19.36 $21.23	$59.70 $59.09	6/30/06	Merck
Hepatitis B-Adult•	ENGERIX-B®	1 dose vials 5 pack - 1 dose T-L syringes, No Needle	$24.25 $24.25	$51.38 $50.35	6/30/06	GlaxoSmithKline
Pneumococcal Polysaccharide (23 Valent)	Pneumovax®	10 pack of 5 dose vials	$14.00	$24.19	6/30/06	Merck
Tetanus & Diphtheria Toxoids¤^	Tetanus & Diphtheria Toxoids Adsorbed for Adults	15 dose vials	$9.75	$14.99	6/30/06	Massachusetts Biologic Labs (Henry Schein Inc.)

/ Vaccine cost includes $2.25 dose Federal Excise Tax
Vaccine cost includes $3.00 per dose Federal Excise Tax
^ Vaccine cost includes $1.50 per dose Federal Excise Tax
* Vaccine cost includes $3.75 per dose Federal Excise Tax
• Vaccine cost includes $0.75 per dose Federal Excise Tax
¤ Vaccines which contain Thimerosal as a preservative

Influenza Vaccine Price List – 11/8/05

Vaccine	Brandname/ Tradename	Packaging	CDC Cost/ Dose	Private Sector Cost/ Dose	Contract End Date	Manufacturer
Influenza ¤ •	Fluzone®	10 dose vials	$9.71	$10.70	2/28/06	sanofi pasteur
Influenza •	Fluzone® Pediatric dose Preservative-free	10 pack - 1 dose syringes	$12.02	$13.00	2/28/06	sanofi pasteur
Influenza •	FluMist®	10 pack – 1 dose sprayers	$17.24	$18.95 to $19.95	2/28/06	MedImmune

/ Vaccine cost includes $2.25 dose Federal Excise Tax
Vaccine cost includes $3.00 per dose Federal Excise Tax
^ Vaccine cost includes $1.50 per dose Federal Excise Tax
* Vaccine cost includes $3.75 per dose Federal Excise Tax
• Vaccine cost includes $0.75 per dose Federal Excise Tax
¤ Vaccines which contain Thimerosal as a preservative

Translations of Foreign-Language Terms

Table 1: Vaccines and Biologics Used in the U.S. and Foreign Markets. This table lists many vaccine products that are (or have been) used in the U.S. and in international markets. It is organized alphabetically by product or trade name. Products known to be no longer in use are marked with an asterisk (*).

Table 2: Translation of Vaccine-Related Terms. This table contains many terms found on immunization records of persons vaccinated in foreign countries, along with their English equivalents. In many cases the term refers to the name of the disease.

Table 3: Vaccine-Related Terms using the Cyrillic Alphabet. This table lists Russian and Ukranian words using the Cyrillic alphabet. Transliteration of Cyrillic characters into Latin letters is difficult, because there is no international agreement among experts on a unified system of converting from the Cyrillic to the Latin alphabet.

Table 4: Translation of Disease Terms into Several Indo-European Languages and Somali.

Table 5: Translation of Disease Terms into Western European and Scandinavian Languages.

These tables were originally developed by the Minnesota Department of Health Immunization Program, and are now maintained and available online through the Immunization Action Coalition (**http://www.immunize.org/izpractices/p5120.pdf** and **http://www.immunize.org/izpractices/p5121.pdf**).
Thanks also to the Washington State Department of Health's Immunization Manual (**http://www.doh.wa.gov/cfh/immunize/documents/schmanul.pdf**), Appendix E.

These lists are not comprehensive and, although we have checked and rechecked our sources, we do not claim complete accuracy.

Table 1: Vaccines and Biologics Used in U.S. and International Markets

This table lists many vaccine products that are (or have been) used in the U.S. and in international markets. While we have checked and rechecked our sources for this information, we do not claim complete accuracy. **November 2004**

Product or Trade name	Antigen(s)	Manufacturer (country)
A.D.T.	Diphtheria, tetanus (adsorbed)	Commonwealth (Australia)
A.K.D.S.	Diphtheria, tetanus, pertussis	_____ (U.K.)
AC Vax	Meningococcus (polysaccharide)	GSK (U.K.)
Acel-Imune *	Diphtheria, tetanus, (acellular) pertussis	WYE (U.S.)
Acelluvax	Pertussis (acellular)	Chiron (Italy)
ACTAcel	Diphtheria, tetanus, pertussis, Hib	AVP (Argentina)
ActHIB	Haemophilus influenzae type b (PRP-T)	AVP (U.S.)
Adimvira A+B	Influenza (whole virus)	Imuna
Admun	Influenza (whole virus)	Duncan
Admune GP	Influenza (whole virus)	Duncan
Agrippal	Influenza	Socopharm
Aimmunogen	Hepatitis A (inactivated)	Chemo-Sero-Therapeutic Resh Inst (Japan)
Aldiana	Diphtheria (absorbed)	Sevac (Czechoslovakia)
Alditeana	Diphtheria, tetanus (absorbed)	Sevac (Czechoslovakia)
Alditerpera	Diphtheria, tetanus (adsorbed), pertussis	Sevac (Czechoslovakia)
Alorbat	Influenza (whole virus)	Asta Pharma
Alteana Sevac	Tetanus	Institute of Sera and Vaccines
Amaril	Yellow fever	AVP (France)
AMC	*Haemophilus influenz*ae, type b	_____ (Cuba)
Anadifterall	Diphtheria (adsorbed)	CHIR (Italy)
Anatetall	Tetanus (adsorbed)	CHIR (Italy)
Arilvax	Yellow fever	MEDI (U.K.)
Attenuvax *	Measles (live, further attenuated)	MRK (U.S.)
AVAC-1, AVA	Anthrax	(for U.S. military use)
AVAXIM	Hepatitis A	AVP (_____)
B-CAPSA *	*Haemophilus influenzae* type b (polysaccharide, 1987 to 1989)	Mead Johnson (U.S.)
BayGam	Human immunoglobulin	Bayer Corporation (U.S.)
BayHep B	Hepatitis B immune globulin (human)	Bayer Corporation (U.S.)
BayRab	Rabies immune globulin	Bayer Corporation (U.S.)
BayTet	Tetanus immune globulin (human)	Bayer Corporation (U.S.)

* = product no longer distributed in U.S.

Product or Trade name	Antigen(s)	Manufacturer (country)
B-CAPSA	*Haemophilus influenzae* type b (1987-1989)	Mead Johnson
BCG	Tuberculosis	Multiple manfacturers and countries
Begrivac	Influenza (split virus)	CHIR (Germany)
Betagen	Hepatitis B	AVP
B-Hepavac II	Hepatitis B	Merck
Biaflu Zonale	Influenza (whole virus)	Farmabiagini
Biavax II *	Rubella, mumps (live)	MRK (U.S.)
Biavax *	Rubella, mumps (live)	MRK (U.S.)
BIG	Botulism immune globulin (not a vaccine)	
Biken-HB	Hepatitis B (recombinant)	BIK (Japan)
Bimmugen	Hepatitis B (recombinant, adsorbed, yeast derived)	Chemo-Sero-Therapeutic Resh Inst (Japan)
BioThrax	Anthrax (adsorbed)	BPT (U.S.)
Biviraten Berna	Measles, mumps (live)	BER (Switzerland)
BVAC	Botulinum antitoxin	(for U.S. military use)
C.D.T.	Diphtheria, tetanus (pediatric, adsorbed)	Commonwealth (Australia)
Celluvax	Pertussis (acellular)	CHIR (Italy)
Cendevax *	Rubella (live) 3/70 to 1976	RIT/SmithKline & French (U.S.)
Certiva *	Diphtheria, tetanus, (acellular) pertussis	Baxter Hyland (U.S.)
Cocqueluchéau	Pertussis (adsorbed)	AVP (France)
Comvax	Hepatitis B, *Haemophilus influenza* type b	MRK (U.S.)
Daptacel	Diphtheria, tetanus, (acellular) pertussis	AVP (U.S.)
D.S.D.P.T.	Diphtheria, tetanus, pertussis (adsorbed)	Dong Shin Pharm (Korea)
D.T. Bis Rudivax	Diphtheria, tetanus, rubella	AVP (France)
Di Te Per Pol Impfstoff	Diphtheria, tetanus, pertussis, polio	BER (Switzerland)
Di-Te-Pol	Diphtheria, tetanus, polio	Statens Seruminstitut (Denmark)
Dif-Tet-All	Diphtheria, tetanus	CHIR (Italy)
DIFTAVAX	Diphtheria, tetanus	AVP (_____)
DiTe Anatoxal	Diphtheria, tetanus (adsorbed)	BER (Switzerland)
Ditoxim	Diphtheria, tetanus (adsorbed)	Dong Shin Pharm (Korea)
Double Anigen B.I.	Diphtheria, tetanus	Bengal Immunity Co (India)
Dryvax	Smallpox	WYE (U.S.)
DT	Diphtheria, tetanus (for pediatric use)	AVP (U.S.)
DT *	Diphtheria, tetanus (for pediatric use)	WYE (U.S.)

* = product no longer distributed in U.S.

Product or Trade name	Antigen(s)	Manufacturer (country)
DTPolio	Diphtheria, tetanus, polio	AVP
DT TAB	Diphtheria, tetanus, *Salmonella typhi, Paratyphi A & B*	AVP (France)
DTaP (generic)	Diphtheria, tetanus, (acellular) pertussis	AVP, WYE, GSK (U.S.)
DTwP (generic) *	Diphtheria, tetanus, (whole-cell) pertussis	AVP, WYE, GSK (U.S.)
Dual Antigen SII	Diphtheria, tetanus (adsorbed)	Serum Institute of India (India)
Ecolarix *	Measles, rubella (live)	RIT/SmithKline (U.S.)
eIPV	Polio (inactivated, enhanced potency)	AVP (U.S.)
Elvarix	Influenza (split virus)	VEB Sachsesches Serumwerk Dresden
Encepur	Tick-borne encephalitis	Chiron (Europe)
Engerix-B	Hepatitis B	GSK (U.K., U.S.)
Enivac-HB	Hepatitis B (Recombinant DNA)	Centro de Ingenieria Genetica Y Biotecnologia (Cuba)
Enterovaccino	Typhoid (IM)	Isi
Epaxal Berna	Hepatitis A - virosomal vaccine	BER (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)
Flu Shield *	Influenza	WYE (U.S.)
Fluad, Agrippal-S1	Influenza	CHIR (Italy)
Fluarix	Influenza	GSK
Flubron	Influenza (whole virus)	Pfizer
FluMist	Influenza (live, attenuated, intranasal)	MEDI (U.S.)
Fluogen *	Influenza	PD (U.S.)
Fluvirin	Influenza	EVN (U.S.)
Fluvirine	Influenza	CellTech Pharma SA
Fluzone	Influenza	AVP (U.S.)
FOH-M	Polio (Inactivated)	(Russia)
FrocuoOke	Polio (Inactivated)	(Russia)
FSME-IMMUNE	Tick-borne encephalitis	Baxter (Austria)
Funed-CEME	Diphtheria, tetanus, pertussis	Belo Horizonte (Brazil)
Gen H-B-Vax	Hepatitis B	Merck-Behringwerke
GenHevac B Pasteur	Hepatitis B	AVP (_____)

* = product no longer distributed in U.S.

Product or Trade name	Antigen(s)	Manufacturer (country)
Gripax	Influenza (whole virus)	Hebrew University
Gripe	Influenza (whole virus)	(Spain)
Gripovax	Influenza (whole virus)	GSK
Gunevax	Rubella	CHIR (Italy)
HAVpur	Hepatitis A	Chiron (Germany)
Havrix	Hepatitis A	GSK (U.K., U.S.)
H-BIG	Hepatitis B immune globulin	NABI, Bayer Corporation (U.S.)
HB Vax Pro	Hepatitis B	AVP
HbOC	Chemical abbreviation for HibTITER	WYE (U.S.)
HBY	Hepatitis B (recombinant)	KGC (Japan)
Hepacare	Hepatitis B (recombinant)	Medeva
Hepaccine-B	Hepatitis B (plasma derived)	Chiel Jedang (South Korea)
Hepavax-B	Hepatitis B (plasma derived)	Korea Green Cross (South Korea)
Hepavax-Gene	Hepatitis B (recombinant DNA)	Korea Green Cross (South Korea)
Heprecomb	Hepatitis B (yeast derived)	BER (Switzerland)
Heptavax B *	Hepatitis B (plasma-derived) 1982 to ___	MRK (U.S.)
Hevac B	Hepatitis B (plasma derived)	AVP (France)
Hexavac	Diphtheria, tetanus, pertussis, polio, hepatitis B, Hib	AVP (Europe)
Hiberix	Hib conjugate	
HIBest	*Haemophilus influenzae* type b	AVP
HibTITER	*Haemophilus influenzae* type b (HbOC)	WYE (U.S.)
Hinkuys karokoe	Pertussis (adsorbed)	Natl. Public Health Institute (Finland)
HPV-77; DK-5	Rubella (live) 1969-1979	MRK (U.S.)
HPV-77; DK-12	Rubella (live) 1970-1973	MRK (U.S.)
HRIG	Rabies immune globulin	AVP; Bayer Corporation (U.S.)
Humotet-anti Tetanus	Tetanus	Wellcome (U.K.)
Hyper-Tet (now called "BayTet")	Tetanus immune globulin	Bayer Corporation (U.S.)
IBV	Polio (inactivated)	Statens Seruminstitut (Denmark)
Immugrip	Influenza	Pierre Fabre Médicament
Immune Globulin Intramuscular (Human)	Broad-spectrum immune globulins	MA, BPT, New York Blood Ctr, Bayer Corporation, CEN (U.S.)
Immunil	Pneumococcal (polysaccharide)	Sidus
Imogam Rabies - HT	Rabies immune globulin	AVP (U.S.)

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Product or Trade name	Antigen(s)	Manufacturer (country)
Imovax	Rabies	AVP (U.S.)
Imovax Parotiditis	Mumps	AVP (France)
Imovax Polio	Polio	AVP (France)
Imovax Sarampion	Measles	AVP (France)
Imovax D.T.	Diphtheria, tetanus	AVP (_____)
Imovax Gripe	Influenza	AVP (_____)
Imovax R.O.R.	Measles, rubella, mumps (live)	AVP (France)
Imovax Rubeola	Measles	AVP (International)
Imovax Mumps	Mumps	AVP (_____)
Imovax Oreillons	Mumps	AVP (France)
Imovax Rabies I.D.	Rabies vaccine (HDCV)	AVP (U.S.)
Imovax Rabies I.M.	Rabies vaccine (HDCV)	AVP (U.S.)
Infanrix	Diphtheria, tetanus, (acellular) pertussis	GSK (Belgium, U.S.)
Infanrix Hexa	DTaP, polio, Hib, hepatitis B	GSK (France)
Infanrix Quinta	DTaP, polio, Hib	GSK (France)
Infanrix Tetra	DTaP, polio	GSK (France)
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
Invirin	Influenza (whole virus)	GSK
Ipad TP	Tetanus, polio	AVP (France)
IPOL	Polio (enhanced potency, inactivated)	AVP (U.S.)
IPV	Polio (inactivated)	General term for inactivated polio vaccine
Isiflu Zonale	Influenza (whole virus)	Isi
Istivac	Influenza	AVP (_____)
JE-VAX	Japanese encephalitis	AVP (U.S.)
Kaksoisrokote Dubbelvaccin	Diphtheria, tetanus (adsorbed)	Natl. Public Health Institute (Finland)
Kikhoste-Vaksine	Pertussis	Statens Institutt for Folkehelse (Norway)
Krztuscowi	Pertussis	(Poland)
Ksztu	Pertussis	(Poland)
Lancy Vaxina *	Smallpox	Swiss Serum and Vaccine Institute (Switzerland)

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Product or Trade name	Antigen(s)	Manufacturer (country)
Lavantuu tirokote	Typhoid	Central Pub Health Lab (Finland)
Liovax *	Smallpox	CHIR (Italy)
Lirubel *	Measles, rubella (live) 4/74 to 6/78	Dow/PitneyMoore (U.S.)
Lirugen	Measles	AVP (Int'l)
Lirugen *	Measles (live) 2/65 to 6/78	Dow (U.S.)
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)
LYMErix *	Lyme disease	GSK (U.S.)
Lyovac Attenuvax *	Measles (live, attenuated)	MRK (U.S.)
Lyovac Meruvax *	Rubella (live)	MRK (U.S.)
M-R Vax II *	Measles, rubella (live)	MRK (U.S.)
M-Vax *	Measles (live) 5/63 to 1979	WYE (U.S.)
Masern-Impfstoff SSW	Measles (live)	_____ (Germany)
Measles Vaccine DK3 *	Measles (live) 1964 to 1972	Philips Roxane, Inc. (U.S.)
Measles *	Measles (inactivated) 1963 to 1966 Measles (live) 12/64 to 1974	Eli Lilly (U.S.)
Mencevax A	Meningococcus (polysaccharide) (Group A)	SmithKline/RIT (Belgium)
Mencevax AC	Meningococcal quadravalent	
Meningitec	Meningococcus (conjugate) (Group C)	WYE (U.K., Australia)
Meninvact	Meningococcus (conjugate) (Group C)	AVP
Menjugate	Meningococcus (conjugate) (Group C)	Socopharm
Menomune-A/C/Y/W-135	Meningococcus (polysaccharide) (Groups A,C, Y, W-135)	AVP (U.S.)
Menpovax 4	Meningococcus (polysaccharide) (Groups A & C)	CHIR (Italy)
Menpovax A+C	Meningococcus (Groups A & C)	CHIR (Italy)
Meruvax *	Rubella (live) 6/69 to ____	MRK (U.S.)
Meruvax II	Rubella (live)	MRK (U.S.)
Mevilin-L *	Measles (live)	Glaxo Operations
MFV	Influenza (whole virus)	Servier
MFV-Ject	Influenza (whole virus)	AVP
MMR *	Measles, mumps, rubella (live) 6/71 to ____	MRK (U.S.)
MMR (generic) *	Measles, mumps, rubella (live) 4/74 to 6/78	Dow Chemical (U.S.)
M-M-R II	Measles, mumps, rubella (live)	MRK (U.S.)

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Product or Trade name	Antigen(s)	Manufacturer (country)
Moniarix	Pneumococcal (polysaccharide)	SmithKline/RIT (Belgium)
Monovax	BCG	AVP
Mopavac Sevac	Measles, mumps (live, attenuated)	Institute of Sera and vaccines (Czechoslovakia)
MOPV *	Polio (live, Sabin, monovalent types I, II, III)	WYE (U.S.)
Morbilvax	Measles (live, attenuated)	CHIR (Italy)
Morubel	Measles, rubella (live, attenuated)	CHIR (Italy)
Moruman Berna	Measles immunglobulin	BER (Switzerland)
Morupar	Measles, mumps, rubella (live, attenuated)	CHIR (Italy)
Movivac	Measles (live, attenuated)	____ (Czechoslovakia)
M-R VAX *	Measles, rubella (live) 7/71 to ____	MRK (U.S.)
Mumaten Berna	Mumps (live)	BER (Switzerland)
Mumps (generic) *	Mumps (live) 4/74 to 6/78	Dow Chemical (U.S.)
Mumps (generic) *	Mumps (inactivated) 1950 to 1978	WYE (U.S.)
Mumps (generic) *	Mumps (inactivated) 1950 to 1977	Eli Lilly (U.S.)
Mumpsvax *	Mumps (live)	MRK (U.S.)
Munevan	Influenza (whole virus)	Medeva
Mutagrip	Influenza	AVP (_____)
Nabi-HB	Hepatitis B immune globulin	NABI (U.S.)
Neis Vac-C	Meningococcus (conjugate) (Group C)	Shire Biologics (Canada)
Neotyf	Typhoid (oral)	Biocine
Nivgrip	Influenza (whole virus)	Nicolau Institute of Virology
NorHOMHerHTA	Polio (Inactivated)	(Russia)
Nothav	Hepatitis A	CHI (Italy)
Okarix	Varicella. live attenuated	AVP
OmniHIB *	*Haemophilus influenzae* type b (PRP-T)	GSK, AVP (U.S.)
OPV	General term for oral polio vaccine	
Orecchioni	Mumps	(Italy)
Orimune *	Polio vaccine (oral, trivalent)	WYE (U.S.)
Ospa	Smallpox	(Poland)
Parionix	Mumps (live)	SmithKline/RIT (Belgium)
Passjura	Mumps	(Sweden)
Pavivac-Sevac	Mumps (live)	Institute of Immunology (Croatia)
PCV, PCV7	General term for pneumococcal conjugate (7-valent)	

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Product or Trade name	Antigen(s)	Manufacturer (country)
Pediacel	DTaP, Hib, IPV	(Europe)
Pediarix	Diphtheria, tetanus, (acellular) pertussis, hepatitis B, IPV	GSK (U.S.)
PedvaxHIB	*Haemophilus influenzae* type b (PRP-OMP)	MRK (U.S.)
Penta	Diphtheria, tetanus, (acellular) pertussis, Hib, IPV	AVP (Canada)
PENT-HIBest	Diphtheria, tetanus, pertussis, polio, Hib	AVP
Pentacel	Diphtheria, tetanus, pertussis, polio, Hib	AVP (Canada)
Pentacoq	Diphtheria, tetanus, pertussis, polio, Hib	AVP (_____)
PENTAct-HIB	Diphtheria, tetanus, pertussis, polio, Hib	AVP (_____)
Pentavac	Diphtheria, tetanus, pertussis, polio, Hib	AVP (_____)
Pentavalente	Diphtheria, tetanus, pertussis, hepatitis B, Hib	_____ (Mexico)
Pentavalenti	Diphtheria, tetanus, pertussis, polio, Hib OR Diphtheria, tetanus, pertussis, polio, hepatitis B	_____ (Italy)
Pfizer Vax-Measles K *	Measles (inactivated) 3/63 to 1970	Pfizer (U.S.)
Pfizer Vax-Measles L *	Measles (live) 2/65 to 1970	Pfizer (U.S.)
Pluserix	Measles, mumps, rubella	GSK (_____)
Pneumopur	Pneumococcal (polysaccharide)	Chiron (Germany)
Pneumovax 23	Pneumococcal (polysaccharide)	MRK (U.S.)
PNU-IMUNE 23 *	Pneumococcal (polysaccharide)	WYE (U.S.)
POLIAcel	Diphtheria, tetanus, pertussis, polio, HIB	AVP (Argentina)
PPV, PPV23	General term for pneumococcal polysaccharide (23-valent)	
Prevenar	Pneumococcal (7-valent, conjugate)	WYE (France)
Previgrip	Influenza	Chiron France
Prevnar	Pneumococcal (7-valent, conjugate)	WYE (U.S.)
Priorix	Measles, mumps, rubella (live)	GSK (U.K.)
ProHIBiT *	*Haemophilus influenzae* type b (PRP-D)	AVP (U.S.)
PRP-OMP	Chemical abbreviation for PedvaxHIB	
PRP-T	Chemical abbreviation for ActHIB	
Pulmovax	Pneumococcal (polysaccharide)	Merck
Purivax *	Polio (inactivated) 1956 to 1965	MRK (U.S.)
QUADRAcel	Diphtheria, tetanus, pertussis, polio	AVP (Argentina)
QUADRAcel/Hibest	Diphtheria, tetanus, pertussis, polio, Hib	AVP (Argentina)
Quadravax	DTP + polio	GSK

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Product or Trade name	Antigen(s)	Manufacturer (country)
Quadrigen *	DTP + polio (1959-1968)	PD (U.S.)
Quatro-Virelon	Diphtheria, tetanus, polio	CHI (Germany)
Quintuple	Diphtheria, tetanus, pertussis, Hib, Polio	GSK (Mexico)
R-HB Vaccine	Hepatitis B (recombinant)	Mitsubishi Chem Corp (Japan)
R-VAC	Rubella (live)	Serum Institute (India)
RA27/3	Rubella (live)	MRK (U.S.)
RabAvert	Rabies (PCEC)	CHI (U.S.)
Rabdomune	Rabies	Impdfstofwerke
Rabipur	Rabies	Chiron
Rabivac	Rabies	Chiron
Rasilvax	Rabies	Chiron
RDCV	Rabies	
Recombivax HB	Hepatitis B (recombinant)	MRK (U.S.)
Repevax	DTaP, IPV	AVP
Respigam, RSV-IVIG	Respiratory syncytial virus immune globulin (not a vaccine)	MEDI (U.S.)
Revaxis	Td, IPV	AVP
RIG (generic)	Rabies immune globulin	Bayer Corporation, AVP (U.S.)
Rimevax	Measles (live)	SmithKline/RIT (Belgium)
Rimparix	Measles (live)	SmithKline/RIT
RIT - LM-2	Measles, mumps (live)	Dong Shin Pharm (Korea)
RIT - LM-3	Measles, mumps, rubella (live)	Dong Shin Pharm (Korea)
RotaShield, RRV-TV *	Rotavirus — 8/98 to 7/99	WYE (U.S.)
Rouvax	Measles (live, attenuated)	AVP (France)
Rubeaten Berna	Rubella (live)	BER (Switzerland)
Rubella (generic) *	Rubella (live) 12/69 to 1972	Philips Roxane (U.S.)
Rubellovac	Rubella	CHIR (Germany)
Rubelogen *	Rubella (live) 12/69 to 1972	PD (U.S.)
Rubeovax *	Measles (live) 2/63 to 1971	MRK (U.S.)
Rudi-Rouvax	Measles, rubella (live)	AVP (France)
Rudivax	Rubella (live, attenuated)	AVP (France)
RVA (generic)	Rabies vaccine adsorbed	BP (U.S.)
Sabin	General term for oral (live) polio vaccine	
Sahia	Polio (live, oral)	Multiple manufacturers

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Product or Trade name	Antigen(s)	Manufacturer (country)
Salk	General term for injectable (inactivated) polio vaccine	
Sandovac	Influenza	Sandoz (Germany)
Serobacterin *	Pertussis – 1945 to 1954	MRK (U.S.)
Sii Triple Antigen	Diphtheria, tetanus, pertussis	Serum Institute (India)
Stamaril	Yellow fever (live, attenuated)	AVP (France)
Streptopur	Pneumococcal (polysaccharide)	Chiron (Italy)
Subinvira	Influenza (split virus)	Imuna
Synagis (palizivumab)	Respiratory syncytial virus immune globulin (not a vaccine)	MEDI (U.S.)
T. Polio	Tetanus toxoid, polio	AVP (Canada)
T.A.B.	Typhoid, paratyphoid (A & B)	- Institute Pasteur (Tunisia) - _____ (Egypt) - Pharmaceutical Industries Corp. (Burma)
T-Immun	Tetanus (adsorbed)	____ (Austria)
Td (generic)	Tetanus, diphtheria (adult formulation)	AVP, BP (U.S.)
Te/Vac/Ptap	Tetanus	_____ (Yugoslavia)
Te Anatoxal	Tetanus	BER (Europe)
Telvaclptap	Tetanus	_____ (Yugoslavia)
Tet-Aktiv	Tetanus	Tropon-Cutter
Tetagrip	Tetanus, influenza	AVP (France)
Tetamun SSW	Tetanus (fluid, nonadsorbed)	Veb Sachsisches Serumwerk (Germany)
Tetamyn	Tetanus	Bioclon, S.A. De C.V. (Mexico)
Tetanol	Tetanus (adsorbed)	CHIR (Germany)
Tetasorbat SSW	Tetanus (adsorbed)	Veb Sachsisches Serumwerk (Germany)
Tetavax	Tetanus (adsorbed)	AVP (France)
Tetracoq 05	Diphtheria, tetanus, pertussis, polio	AVP (France)
TetrAct-HIB	Diphtheria, tetanus, pertussis, Hib	AVP (_____)
Tetramune *	Diphtheria, tetanus, pertussis, Hib	WYE (U.S.)
Tetravac Acellulaire	Diphtheria, tetanus, pertussis, polio	AVP
Tetravalenti	Diphtheria, tetanus, pertussis, hepatitis B	_____ (Italy)
Tetravax *	Diphtheria, tetanus, pertussis, polio - 1959 to 1965	MRK (U.S.)
Tice BCG	Bacillus Calmette-Guérin vaccine (for TB)	OTC (U.S.)
Ticovac	Tick-borne encephalitis	Baxter SA
TIG	Tetanus immune globulin (generic)	Bayer Corporation (U.S.)

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Product or Trade name	Antigen(s)	Manufacturer (country)
Tifovax	Typhoid	
TOPV	Trivalent oral polio vaccine	Multiple manufacturers and countries
Titifica	Typhoid and para typhoid	_____ (Italy)
Tresivac Lyopholized	Measles, mumps, rubella	Serum Institute (India)
Triacel	Diphtheria, tetanus, (acellular) pertussis	AVP (_____)
Triacelluvax	Diphtheria, tetanus, (acellular) pertussis	CHIR (Europe)
TriHIBit	Diphtheria, tetanus, (acellular) pertussis, Hib	AVP (U.S.)
Tri-Immunol *	Diphtheria, tetanus, pertussis	WYE (U.S.)
Trimovax	Measles, mumps, rubella (live)	AVP (France)
Trinivac *	Diphtheria, tetanus, pertussis – 1952 to 1964	MRK (U.S.)
Tripacel	Diphtheria, tetanus, (acellular) pertussis	AVP (_____)
Tripedia	Diphtheria, tetanus, (acellular) pertussis	AVP (U.S.)
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)
Tritanrix	DTwP	GSK
Tritanrix-HB	DTwP/hepatitis B	GSK
Tritanrix-HB-Hib	DTwP/hepatitis B/Hib	GSK
Trivacuna Leti	Diphtheria, tetanus (adsorbed), pertussis	Laboratory Leti (Spain)
Trivax	Diphtheria, tetanus (plain), pertussis	Wellcome (U.K.)
Trivax-ad	Diphtheria, tetanus (adsorbed), pertussis	- EVN (UK) - Wellcome (UK)
Trivax-Hib	Diphtheria, tetanus, pertussis, Hib	GSK (UK)
Trivb	Diphtheria, tetanus, pertussis	Brazil (_____)
Triviraten	Measles, mumps, rubella (live, attenuated)	BER (Switzerland)
Trivivac *	Diphtheria, tetanus, pertussis	MRK (U.S.)
Trivivac Sevac	Measles, mumps, rubella (live, attenuated)	Institute of Sera & Vaccines (Czechoslovakia)
TT	Tetanus toxoid (generic)	AVP (U.S.)
TT vaccine	Tetanus toxoid (adsorbed)	_____ (India)
Tussitrupin Forte	Pertussis	Staatliches Institut (Germany)
Twinrix	Hepatitis A & B (adult formulation)	GSK (U.K., U.S.)
Twinrix Junior	Hepatitis A & B (pediatric formulation)	GSK (U.S.)
Ty21a (Vivotif Berna)	Typhoid (live, oral, lyophilized)	BER (Switzerland)
Tyne	Tuberculosis (BCG)	Sweden
Typherix	Typhoid	GSK (U.K.)

Product or Trade name	Antigen(s)	Manufacturer (country)
Typhim Vi (ViCPs)	Typhoid (parenteral, injectable)	AVP (U.S., France)
Typhoid Vaccine *	Typhoid (inactivated, parenteral)	WYE (U.S.)
Typhopara-typhoidique	Typhoid and para typhoid	___ (France)
VA-Mengoc-BC	Meningococcal (Groups B & C)	Finlay Vacunas y Sueros Centro de Investigation (Cuba)
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)
Vaccinum Morbillorum Vivum	Measles (live)	Moscow Research Institute (Russia)
Vacina Triplice Viral	Measles, mumps, rubella	_____ (Brazil)
Vacina Triplice	Diphtheria, tetanus, pertussis	Instituto Butantan (Brazil)
Vacina Dupla	Diphtheria, tetanus	Instituto Butantan (Brazil)
Vaksin Cacar	Smallpox	___ (Indonesia)
Vaksin Serap	Diphtheria, tetanus, pertussis	Perum Bio Farma (Indonesia)
Vaksin Campak Kerig	Measles (live, attenuated)	Pasteur Institute (Indonesia)
Vaksin Kotipa	Cholera, typhoid and paratyphoid A, B & C	Perum Bio Farma (Indonesia)
Vamoavax	Measles, mumps (live)	Institute of Immunology (Croatia)
Vaqta	Hepatitis A (inactivated)	MRK (U.S.)
Varicellon	Varicella zoster immunoglobulin	Behringwerke Aktiengesellischaft (Germany)
Varie	Smallpox (lyophilized)	Institute of Sera and Vaccine (Czechoslovakia)
Varilrix	Varicella (live, Oka strain)	GSK (Australia, Belgium)
Varivax	Varicella (live)	MRK (U.S.)
Vaxem-Hib	*Haemophilus influenzae* type b	CHIR (Italy)
Vaxicoq	Pertussis (adsorbed)	AVP (France)
Vaxigrip	Influenza	AVP (_____)
Vaxipar	Mumps (live)	CHIR (Italy)
VCDT	Diphtheria, tetanus	Cantacuzino Institute (Romania)
VDA Vaccin Difteric Adsorbit	Diphtheria	Cantacuzino Institute (Romania)
ViCPs (Typhim Vi)	Typhoid (inactivated, injectable)	AVP (U.S.)
VIG	Variola (smallpox) immune globulin (not a vaccine)	Distributed by CDC
Virelon C	Polio (Inactivated)	Chiron (Germany)
Virelon T 20	Polio (live, oral, trivalent)	Behringserke Aktiengesellischaft (Germany)

* = product no longer distributed in U.S.

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Product or Trade name	Antigen(s)	Manufacturer (country)
Virovac Massling, Perotid, Rubella	Measles, mumps, rubella	_____ (Sweden)
Vivotif Berna (Ty21a)	Typhoid (oral, live)	BER (Switzerland)
VT (Vacina Triplice)	Diphtheria, tetanus, pertussis	Instituto Butantan (Brazil)
VTV (Vacina Triplice Viral)	Measles, mumps, rubella	_____ (Brazil)
VVR	Measles (live, attenuated)	Cantucuzino Institute (Romania)
VZIG	Varicella zoster immune globulin (generic)	MA (U.S.)
Welltrivax trivalente	Diphtheria, tetanus, pertussis	_____ (Spain)
YF-VAX	Yellow fever	AVP (U.S.)
Zaantide	Diphtheria anti-toxin	Inst. of Immunology (Croatia)
Zaantite	Tetanus anti-toxin	Inst. of Immunology (Croatia)
Zaditeadvax	Diphtheria, tetanus	Inst. of Immunology (Croatia)
Zaditevax	Diphtheria, tetanus	Inst. of Immunology (Croatia)
Zamevax A+C	Meningococcus (polysaccharide, Groups A & C)	Inst. of Immunology (Croatia)
Zamovax	Measles (live)	Inst. of Immunology (Croatia)
Zamruvax	Measles, rubella (live)	Inst. of Immunology (Croatia)
Zaruvax	Rubella (live)	Inst. of Immunology (Croatia)
Zatetravax	Diphtheria, tetanus, pertussis, parapertussis	Inst. of Immunology (Croatia)
Zatevax	Tetanus	Inst. of Immunology (Croatia)
Zatribavax	Diphtheria, tetanus, pertussis	Inst. of Immunology (Croatia)
Zatrivax	Measles, rubella, mumps (live)	Inst. of Immunology (Croatia)

*Abbreviations: **AVP** = Aventis Pasteur (includes Connaught Laboratories and Pasteur Mérieux Connaught); **BER** = Berna Products Corporation (includes Swiss Serum and Vaccine Institute Berne); **BIK** = The Research Foundation for Microbial Diseases of Osaka University; **BPT** = BioPort (successor entity for Michigan Biologic Products Institute); **CEN** = Centeon L.L.C. (includes Armour Pharmaceutical Company); **CHIR** = Chiron Corporation (includes Sclavo); **EVN** = Evans Medical Limited; **KGC** = Korea Green Cross Corporation; **GSK** = GlaxoSmithKline (includes ...); **MA** = Massachusetts Public Health Biologic Laboratories; **MEDI** = MedImmune (purchased Aviron); **MRK** = Merck & Co., Inc.; **NABI** = Nabi Pharmaceuticals (formerly North American Biologicals, Inc.); **OTC** = Organon Teknika Corporation; **PJP** = PowderJect Pharmaceuticals; **PD** = Parke Davis; **WYE** = Wyeth Pharmaceuticals, (includes Wyeth-Lederle, Wyeth Laboratories, Lederle Laboratories, Praxis Biologics).

* = product no longer distributed in U.S.

Table 2: Translation of Vaccine-Related Terms

The table below lists many of the terms you will find on immunization records of persons born outside of the U.S., along with their translation into English. In most cases, the term refers to the name of a disease against which the person may have been vaccinated. While we have checked and rechecked our sources for this information, we do not claim complete accuracy. **November 2004**

Term	English Translation	Language
(Anti)	(Against) *name of disease*	Multiple languages
Alhasiba	Rubella	Arabic
Antipolio inattivato	IPV	Italian
AR	Measles	Romania
As'al addeekee	Pertussis	Arabic
Athab	Mumps	Arabic
Bach Hâu	Diphtheria	Vietnamese
Ban Đo	Rubella	Vietnamese
Batok rejan	Pertussis	Malay
Batuk rejan	Pertussis	Indonesian
Beguk	Mumps	Indonesian
Beke	Mumps	Tagalog
Beseže	BCG	Bosnian, Croatian, Serbian
Biring Peluh	Rubella	Indonesian
Błonicy, Bionica	Diphtheria	Polish
BMR	Measles, Mumps, Rubella	Dutch
Bof	Mumps	Dutch
Bornelammelse	Polio	Danish
Bus-buska	Varicella	Somali
Cachumba (papeira)	Mumps	Portuguese
Cagaarshowga A, B	Hepatitis A, B	Somali
Campak	Measles	Indonesian
Chripka	Influenza	Slovak
Cierny kasel	Pertussis	Slovak
Cólera	Cholera	Spanish
Coqueluche	Pertussis	French, Portuguese, Spanish
Cufaa	Tetanus	Oromiffaa (Ethiopia)
Cuno xanuun	Diphtheria	Somali
~~Dabayl~~	~~Poliomyelitis~~	~~Somali~~
Davivy Kasel	Whooping Cough	Czech

Term	English Translation	Language
Detepe	DTP	Bosnian, Croatian, Serbian
Difteeriyaa	Diphtheria	Oromiffaa (Ethiopia)
Difteri	Diphtheria	Swedish, Norwegian, Haitian Creole, Indonesian
Difteria	Diphtheria	Albanian, Arabic, Spanish, Romanian, Portuguese
Diftéria	Diphtheria	Slovak
Difterie	Diphtheria	Czech, Dutch
Difteriei	Diphtheria	Romanian
Difterija	Diphtheria	Bosnian, Croatian, Serbian
Difterite	Diphtheria	Italian
Difteritis	Diphtheria	Danish
(La) Diphtérie	(The) Diphtheria	French
Diphtherie	Diphtheria	German
Dipterya	Diphtheria	Tagalog
Di Te	DT	Romanian
DiTePe	DTP	Slovak
Di-Te-Per	DTP	Romanian
Dječja paraliza	Poliomyelitis	Bosnian, Croatian, Serbian
DKTP	Diphtheria, Tetanus, Pertussis, Inactivated Polio	Dutch
DTC, DT Coq	DTP	French
DTCP	DTP-IPV	French
Duf	Polio	Somali
Duple	Diphtheria, Tetanus	Spanish (Cuba)
Duplex	Diphtheria, Tetanus	Swedish
Dyfteria	Diphtheria	Polish
El Safra	Hepatitis	Arabic
Emofilo b	Hib	Italian
Epatit A, B	Hepatitis A, B	Haitian Creole
Epatite A, B	Hepatitis A, B	Italian
Faaresyge	Mumps	Danish
Febra Galbena	Yellow Fever	Romanian
Fievre jaune	Yellow Fever	French
Flou	Influenza	Haitian Creole

Term	English Translation	Language
Fruthi	Measles	Albanian
Furuq	Smallpox	Somali
Fushin	Rubella	Japanese
Gelekoorts	Yellow Fever	Dutch
Gifira	Measles	Oromiffaa (Ethiopia)
Gifira farangli	Rubella	Oromiffaa (Ethiopia)
Gordelroos	Varicella	Dutch
Gowracato	Diphtheria	Somali
Griep	Influenza	Dutch
(Anti) Gripa	(Against) influenza	Romanian
Gripa	Influenza (flu)	Bosnian, Croatian, Romanian, Serbian
(La) Gripe	(The) influenza	Portuguese, Spanish
Grippe	Influenza	French, German
Gruzlica	Tuberculosis	Polish
Grypa	Influenza	Polish
Gula Febern	Yellow Fever	Swedish
Gurra dhaabsis	Mumps	Oromiffaa (Ethiopia)
Hablobaas	Varicella	Somali
Haemophilus nooca b	*Haemophilus influenzae* type b	Somali
Has 'ba	Measles	Arabic
Hashika	Measles	Japanese
Hashofu	Tetanus	Japanese
Hawb pob	Pertussis	Hmong
Hemófilo tipo b	*Haemophilus influenza*e type b	Spanish
Hepatita A, B	Hepatitis A, B	Romanian
(Anti) Hepatite A, B	(Against) hepatitis A, B	Portuguese
Hepatite A, B	Hepatitis B	French, Portuguese
Hepatitei A, B	Hepatitis A, B	Romanian
Hepatitida	Hepatitis	Czech, Slovak
Hepatitis tipo A, B	Hepatitis A, B	Spanish
Hinkuyska	Pertussis	Finnish
Ho Gà	Pertussis	Vietamese
Holera	Cholera	Romanian
Hri pavac	Pertussis	Serbo-Croatian
Hyakaseki	Pertussis	Japanese

Term	English Translation	Language
Infilowense	Influenza	Somali
Jadeeco	Measles	Somali
Jadeeca Been, Jadeeco Been	Rubella	Somali
Jadeeco jarmalka	Rubella	Somali
Jaykkakouristus	Tetanus	Finnish
Jifuteria	Diphtheria	Japanese
Joonis A	Hepatitis A	Somali
Joonis B	Hepatitis B	Somali
Kabmob siab hom B	Hepatitis B	Hmong
Kašalj hripavac	Pertussis	Croatian
Keuchhusten	Pertussis	German
Kighoste	Pertussis	Danish
Kikhosta	Pertussis	Swedish
Kikhoste	Pertussis	Norwegian
Kinderlähmung	Poliomyelitis	German
Kinderverlamming	Polio	Dutch
Kinkhoest	Pertussis	Dutch
Kix	Pertussis	Somali
Koklich	Pertussis	Haitian Creole
Koklusz	Pertussis	Polish
Kolera	Cholera	Swedish
Kopper	Smallpox	Norwegian
Krzamak	Measles	Slovak
Krztuscowi, Krztusiec	Pertussis	Polish
Kub cer	Diphtheria	Hmong
Kurkkumata	Diphtheria	Finnish
Kusma	Mumps	Norwegian
l'Haemophilus b	*Haemophilus influenzae*, type b	French
Laamsheesaa	Polio	Oromiffaa (Ethiopia)
Lapsihalvaus	Polio	Finnish
Lawoujòl, Laroujòl	Measles	Haitian Creole
Leverbetaendelse	Hepatitis	Danish
Leverbetennelse	Hepatitis	Norwegian
Longontsteking	Pneumonia	Dutch
Male boginje	Rubella	Bosnian, Serbian

Term	English Translation	Language
Malmouton	Mumps	Haitian Creole
Mami	Mumps	Samoan
(Die) Masern	(The) Measles	German
Mässling, Masslingormerly	Measles	Swedish
Mazelen	Measles	Dutch
Meslinger	Measles	Norwegian, Danish
Misela	Measles	Samoan
Morbillo	Measles	Italian
MPR (morbillo, parotote, rosolia)	Measles, Mumps, Rubella	Italian
(La) Numonía	(The) Pneumonia	Spanish
Odra	Measles	Polish
(Les) Oreillons	(The) Mumps	French
Oreion, Oreionului	Mumps	Romanian
Ospa	Smallpox	Polish
Ospice	Measles	Bosnian
Osypky	Measles	Slovak
Otafukukuaze	Mumps	Japanese
Paperas	Mumps	Spanish
Paralisia infantil	Poliomyelitis	Portuguese
Paraliz dzieciecy	Polio	Polish
Parotidite epidémica	Mumps	Portuguese
Parotiditis	Mumps	Spanish
Parotite	Mumps	Italian
Parotitida	Mumps	Czech
Parotitis	Mumps	Slovak
Pässjura	Mumps	Swedish
Penyaakit bengok	Mumps	Malay
Penyakit lumpuh	Polio	Indonesian
Pertosse	Pertussis	Italian
Pertosse acellulare	Acellular Pertussis	Italian
Pertuse	Pertussis	Czech
Pertusis	Pertussis	Tagalog
Pertusisi	Pertussis	Albanian
Pirquet's Reaction	Reaction to TB Skin Test	Multiple

Term	English Translation	Language
Pljuskavice, Kozice	Varicella	Serbian
Pneumoniei	Pneumonia	Romanian
Pocken	Smallpox	German
Podstawowe	Primary	Polish
Pojar German	Rubella	Romanian
Pojarul, Pojarului	Measles	Romanian
Pokken	Smallpox	Dutch
Polio	Polio	Swedish
Poliomielite	Poliomyelitis	Italian, Portuguese
Poliomielitic	Poliomyelitis	Romanian
Poliomielitis	Poliomyelitis	Spanish
Poliomyélite	Polio	French
Poliomyelitis	Polio	Czech
Poliomyelitt	Polio	Norwegian
Polmonite	Pneumonia	Italian
Polyo	Polio	Haitian Creole, Tagalog
Polyomyelitida	Polio	Slovak
Priusnica	Mumps	Slovak
Przypominajace	Booster	Polish
Pulmonía	Pneumonia	Spanish
Qaamow-Qashiir	Mumps	Somali
Qaaxo-Tiibii	Tuberculosis	Somali
Qakkee	Pertussis	Oromiffaa (Ethiopia)
Qanja Barar	Mumps	Somali
Qhua Maj	Rubella	Hmong
Qhua Pias	Measles	Hmong
Qog	Mumps	Hmong
Quai Bi	Mumps	Vietnamese
Radang hati	Hepatitis	Indonesian
Ribeyòl	Rubella	Haitian Creole
Rode hond	Rubella	Dutch
Röda Hund	Rubella	Swedish
Rode Hunde	Rubella	Danish
Røde hunder	Rubella	Norwegian
ROR	Measles, Mumps, Rubella	French
Rosolia	Rubella	Italian

Term	English Translation	Language
Rötein	Rubella	German
(La) Rougeole	(The) Measles	French
Rozyczka	Rubella	Polish
Rubeola	Rubella	Bosnian
Rubéola	Rubella	Spanish
Rúbéola	Rubella	Portuguese
Rubéole	Rubella	French
Rubeolei, Rubeola	Rubella	Romanian
Rujeola, Rujeolei	Measles	Romanian
Rupela	Rubella	Samoan
Ruzienka	Rubella	Slovak
Sài Uon Ván	Tetanus	Vietamese
Sakit champak	Measles	Malay
Sakit rengkong	Diphtheria	Malay
Sambabaha	Pneumonia	Somali
(Anti) Sarampión	(Against) measles	Spanish
Sarampión Aleman	Rubella	Spanish
Sarampión Comun	Measles	Spanish
Sarampo	Measles	Portuguese
Saranpyon	Varicella (Chickenpox)	Haitian Creole
Si rubeolei	Rubella	Romanian
Sikotauti	Mumps	Finnish
Sh niamahi	Polio	Japanese
Shel'el	Polio	Arabic
Shimbiraa	Hepatitis	Oromiffaa (Ethiopia)
Smittkoppor	Smallpox	Swedish
Spalnicky	Measles	Czech
So'i	Measles	Vietnamese
Sot Tê Liêt	Polio	Vietnamese
Starrkramph	Tetanus	German
Stelkramp	Tetanus	Swedish
Stijfkramp	Tetanus	Dutch
Stivkrampe	Tetanus	Danish, Norwegian
Subinuira	Influenza	Czech
Swinka	Mumps	Polish
Tallaakla Qaaxada	BCG	Somali

Term	English Translation	Language
Taytano	Tetanus	Somali
Teŕng	Tuberculosis	Dutch
Tetánica	Tetanus	Spanish
Tetânica	Tetanus	Portuguese
Tetano	Tetanus	Italian, Tagalog
Tétano	Tetanus	Portuguese, Spanish
Tetanos	Tetanus	Romanian
(Anti) Tétanos (or AT)	(Against) tetanus	Spanish
Tétanos	Tetanus	French
Tetanòs	Tetanus	Haitian Creole
Tetanosul, Tetanosului	Tetanus	Romanian
Tetanozi	Tetanus	Albanian
Tezec, Tężcowi	Tetanus	Polish
Tigdas	Measles	Tagalog
Tos Ferina	Whooping Cough	Spanish
Tosse Asinina	Whooping Cough	Italian
Triplice	DTP	Portuguese
Trippel	Diphtheria, Tetanus, Pertussis	Sweden
Tuag tes tuag taw	Polio	Hmong
Tubercolosi	Tuberculosis	Italian
Tuberculose	Tuberculosis	French
(Die) Tuberkulose	(The) tuberculosis	German
Tuhkarokko	Measles	Finnish
Tuse convulsiva, Tusei convulsive	Pertussis	Romanian
Ua npuag	Tetanus	Hmong
Upala pluća	Pneumonia	Bosnian, Croatian, Serbian
VAHB	Hepatitis B	Portuguese
VAP	Polio	Portuguese
VAS	Measles	Portuguese
VASPR	MMR	Portuguese
VAT	Tetanus	Portuguese
Vaioloso	Smallpox	Italian
Vannkopper	Varicella	Norwegian
(La) Varicela	(The) chickenpox	Spanish
Varicelă, Varicelei	Varicella (chickenpox)	Romanian

Term	English Translation	Language
Variola, Variolei	Smallpox	Romanian
(La) Variole	(The) Smallpox	French
Veliki boginje	Smallpox	Bosnian, Croatian, Serbian
Veliki kašalj	Pertussis	Bosnian, Serbian
Viêm Gan B	Hepatitis B	Vietnamese
Vihurirokko	Rubella	Finnish
Viruela	Smallpox	Spanish
Vodene kozice	Varicella	Croatian
Wareento	Pneumonia	Somali
Wundstarrkrampf	Tetanus	German
Xiiqdheer	Pertussis	Somali
Zápal' plüc	Pneumonia	Slovak
Zapaljenje	Hepatitis	Serbo-Croatian
Zapalenie płuc	Pneumonia	Polish
Zapalenie watroby	Hepatitis	Polish
Zardenky	Rubella	Czech
Zaškrt	Diphtheria	Czech
Zauške	Mumps	Bosnian
Zaušnjaci	Mumps	Croatian, Serbian
Zei Genpeter	Mumps	German
Žutica A, B	Hepatitis A, B	Bosnian, Croatian, Serbian

Table 3: Vaccine-Related Terms Using Cyrillic Alphabet		
Бцж	BCG	Russian
АКДС	DTP	Russian
Дифтерит, Дифтерия	Diphtheria	Russian
Гемонфлюс инфлюэнцы типа Б	*Haemophilus influenzae* type b	Russian
Гепатит А, В	Hepatitis A, B	Russian
Грипп	Influenza	Russian
Корь	Measles	Russian
Кір	Measles	Ukrainian
Свинка, Паротит	Mumps	Russian
Коклюш	Pertussis	Russian
Воспале лёгких Пневмония	Pneumonia	Russian
Полиомиелит	Polio, Poliomyelitis	Russian
Поліо	Polio	Ukrainian
Краснуха	Rubella	Russian
Оспа	Smallpox	Russian
Столбняк, Столбняка	Tetanus	Russian
Стовбняк	Tetanus	Ukrainian
Туберкулез	Tuberculosis	Russian
Ветрянка	Varicella	Russian
Манту	Mantoux	Russian
Вакцина	Vaccine	Russian
Вакцинация	Series	Russian
Ревакцинация	Booster	Russian

Table 4: Translation of Disease Terms into Indo-European Languages and Somali

English	Bosnian	Croatian	Polish	Romanian	Russian/Ukrainian	Serbian	Slovak	Somali
DTP	Detepe	Detepe		Di-Te-Per	АКДС	Detepe	DiTePe	
Diphtheria	Difterija	Difterija	Błonicy, Bionica	Difteria, Difteriei, Diftrie, Anti Difteriei	Дифтерит, Дифтерия	Difterija	Diftéria	Gowracato
Tetanus	Tetanus	Tetanus	Tężcowi, Tezec	Tetanos, Anti Tetanos, Tetanosul	Столбняк Стовбняк (Uk)	Tetanus	Tetanus	Taytano
Pertussis	Veliki kašalj	Kašalj hripavac	Krztuscowi, Krztusiec	Tuse Convulsiva, Tusei Convulsive	Коклюш	Veliki kašalj	Čierny kašeľ	Xiiqdheer
Poliomyelitis	Dječja paraliza	Dječja paraliza	Poliomyelitis	Poliomielita, Poliomielitic, Poliomielitei	Полиомиелит Полио (Uk)	Dečja paraliza	Poliomyelitis	Dabayl
Measles	Rubeola	Ospice	Odra	Pojarul	Корь Кір (Uk)	Krzamak	Morbilli, Osýpky	Jadeeco
Mumps	Zauške	Zaušnjaci	Swinka	Oreionul, Oreion	Свинка, Паротит	Zaušnjaci	Parotitis	Qaamow-Qashiir, Qanja Barar
Rubella	Male boginje	Rubeola		Rubeola, Rubeolei, Pojar German	Краснуха	Male boginje	Rubeola	Jadeeca Been, Jadeeco Been
Haemophilus influenzae b		Haemophilus influenzae b		Hib, Haemophilus Influenzae de tip b	Гемофилюс инфлюэнцы типа Б			Haemophilus nooca b
Hepatitis B	Žutica B, Hepatitis B	Žutica B, Hepatitis B		Hepatita B, Hepatitei B	Гепатит В	Žutica B, Hepatitis B		Cagaarshowga B, Joonis B
Hepatitis A	Žutica A, Hepatitis A	Žutica A, Hepatitis A		Hepatitei A, Hepatita A	Гепатит А	Žutica A, Hepatitis A		Cagaarshowga A, Joonis A
Varicella	Ospice	Vodene kozice		Varicelei, Varicelă	Ветрянка	Pljuskavice, Kozice	Varicella	Bus-buska, Hablobaas
Influenza	Gripa	Gripa	Grypa	Gripal, Gripa	Грипп	Gripa	Chrípka	Infilowense
Pneumonia	Upala pluća	Upala pluća	Zapalenie pluc	Pneumoniei	Воспаление лёгких Пневмония	Upala pluća	Zápal' plúc	Wareento
Smallpox	Veliki boginje	Veliki boginje	Ospa	Variola, Variolei	Оспа	Veliki boginje		Furuq
Tuberculosis	Tuberkuloza	Tuberkuloza	Gruzlica	Tuberculozei	туберкулез	Tuberkuloza	Tuberkulóza	Qaaxo-Tiibii
Mantoux	Manto Test	Manto Test			Манту	Manto Test		
BCG	Beseže	Beseže			Биж	Beseže		Tallaalka Qaaxada

Table 5: Translation of Disease Terms into Western European Languages

English	French	Dutch	German	Italian	Norwegian	Portuguese	Spanish	Swedish
DTP	DT Coq, DTC	DKTP				Tríplice		Trippel
Diphtheria	Diphtérie	Diphtheria	Diphtherie	Difterite	Difteri	Difteria	Difteria	Difteri
Tetanus	Tétanos	Tetanus	Wundstarrkrampf	Tetano	Stivkrampe	Tétano Tetânica	Tétanos, Tetánica, Tétano	Stelkramp
Pertussis	Coqueluche	Kinkhoest	Keuchhusten	Pertosse	Kikhoste	Coqueluche	Coqueluche	Kikhosta
Whooping Cough				Tosse Asinina			Tos Ferina	
Poliomyelitis	Poliomyélite	Poliomyelitis	Kinderlähmung	Poliomielite	Poliomyelitt	Poliomielite, Paralisia Infantil	Polio/Antipolio, Poliomielitis	Poliomyelitis
MMR	ROR	BMR						
Measles	Rougeole	Mazelen	Masern	Morbillo	Meslinger	Sarampo Rúbéola	Sarampión, Sarampión Comun	Mässling
Mumps	Oreillons	Bof	Zei Genpeter	Parotite	Kusma	Parotidite epidémica, Cachumba	Paperas, Parotiditis	Påssjura
Rubella	- Rubéole - Rubéola	Rode hond	Rötein	Rosolia	Røde hunder	Rúbéola	Rubéola Sarampión Aleman	Röda Hund
Haemophilus influenzae b	l'Haemophilus b	Haemophilus influenzae b	Haemophilus influenzae b	Haemophilus influenzae b	Haemophilus influenzae b	Influenzae Haemophilus tipo B	Hemófilo tipo b, Haemophilus influenzae Tipo B	
Hepatitis B	Hepatite B	Hepatitis B	Hepatitis B	Epatite B		Hepatite B	Hepatitis B	
Hepatitis A	Hepatite A	Hepatitis A	Hepatitis A	Epatite A		Hepatite A	Hepatitis A	
Varicella	Varicella	Gordelroos	Windpocken	Varicella	Vannkopper	Varicela	Varicela	
Influenza	Grippe	Griep	Grippe	Influenzae	Influensa	Gripe	Gripe	Influensa
Pneumonia	Pneumonie	Longontsteking		Polmonite			Pulmonía Numonía	
Smallpox	Variole	Pokken	Pocken	Vaioloso	Kopper		Viruela	Smittkopper
Tuberculosis	Tuberculose	Tering	Tuberkulose	Tubercolosi			Tuberculínica	Tuberkulos

APPENDIX C
Vaccine Storage & Handling

Appendix C

Vaccine Management

Recommendations for Storage and Handling of Selected Biologicals

June 2005

Appendix C

Contents

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.

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 container.

Instructions for Use

Shake vial vigorously before withdrawal and use.

Shelf Life After Opening

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 outdated, if not contaminated.

Special Instructions

Rotate stock so that the earliest dated material is used first.

* 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) notify the Quality Control office at the vaccine manufacturer; and 3) notify your state health department immunization program if vaccine was publicly purchased vaccine.

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

DTaP/HepB/IPV: Diphtheria Toxoid, Tetanus Toxoid, Acellular Pertussis Vaccine, Hepatitis B Vaccine, Inactivated Polio Vaccine—Pediatric

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.

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

Shake well before withdrawal and use. Do not use if resuspension does not occur with vigorous shaking.

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.

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* ActHIB® (sanofi pasteur) should be used within 24 hours of reconstitution if used alone. If sanofi pasteur DTaP 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. Sanofi pasteur DAPTACEL® is not licensed for use in reconstitution of ActHIB®.

** 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) notify the Quality Control office at the vaccine manufacturer; and 3) notify your state health department immunization program if vaccine was publicly purchased vaccine.

HBIG: Hepatitis B Immune Globulin

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.

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 container.

Instructions for Reconstitution or Use

Shake vial vigorously before withdrawal and use.

Shelf Life After Reconstitution or Opening

Use until outdated, if not contaminated.

Special Instructions

Rotate stock so that the earliest dated material is used first.

Hepatitis Vaccines: Hepatitis A, Hepatitis B, Hepatitis A/B, Hepatitis B/*Haemophilus influenzae* type b

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.

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 Use

Shake vial vigorously before withdrawal and use.

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.

* 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) notify the Quality Control office at the vaccine manufacturer; and 3) notify your state health department immunization program if vaccine was publicly purchased vaccine.

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.

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 container.

Instructions for Reconstitution** or Use

Shake vial vigorously before withdrawal and use. Do not use if resuspension does not occur with vigorous shaking.

Shelf Life After Reconstitution** or Opening

The vaccine should be administered shortly after withdrawal from the vial.

Special Instructions

Rotate stock so that the earliest dated material is used first.

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.

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 container.

Instructions for Use

Multidose Vials: Shake vial vigorously before withdrawal and use. Withdraw 0.5 mL of vaccine into separate sterile needle and syringe for each immunization.

Shelf Life After Opening

The vaccine should be administered shortly after withdrawal from the vial. Doses remaining in the vial may be used until outdated if not contaminated.

Special Instructions

Rotate stock so that the earliest dated material is used first.

C

* 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) notify the Quality Control office at the vaccine manufacturer; and 3) notify your state health department immunization program if vaccine was publicly purchased vaccine.

**ActHIB® (sanofi pasteur) should be used within 24 hours of reconstitution if used alone. If sanofi pasteur DTaP 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. Sanofi pasteur DAPTACEL® is not licensed for use in reconstitution of ActHIB®.

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.

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

Formulated for use during current influenza season.

Instructions for Use

Shake vial vigorously before withdrawal and use.

Shelf Life After Opening

Multidose Vials: The vaccine should be administered shortly after withdrawal from the vial.

Manufacturer-Filled Syringes: Sterile until removal of hub cap.

Special Instructions

Rotate stock so that the earliest dated material is used first.

C

* 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) notify the Quality Control office at the vaccine manufacturer; and 3) notify your state health department immunization program if vaccine was publicly purchased vaccine.

LAIV: Live Attenuated Influenza Vaccine

Shipping Requirements

Should be shipped frozen in insulated container with dry ice. at 4°F (-20°C) or colder. Shipment includes WarmMark™ temperature indicator.

Condition upon Arrival*

Should be frozen at 4°F (-20° C) or colder; **must not have thawed in shipment.** (All windows in WarmMark™ indicator should be white. If any indicator windows are red, do not use the product. Call the manufacturer for further instructions.)

Storage Requirements

Upon arrival, immediately store the vaccine in a freezer with its own exterior door. Must be maintained in a continuously frozen state at 5°F (-15°C) or colder. **No freeze/thaw cycles are permitted with this vaccine.** May be stored in either a manual defrost freezer or in a frost-free freezer compartment.

In order to maintain the temperature of 5°F (-15°C) or colder in the freezer, 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 temperatures will be necessary to avoid freezing killed or inactivated vaccines.

NOTE: The manufacturer supplied freezer box is no longer required for storage of LAIV vaccine in a frost-free freezer. This new storage requirement applies to the 2005-2006 influenza season, not the 2004-2005 LAIV vaccine supply.

Shelf Life

Formulated for use during current influenza season.

Instructions for Use

Thaw sprayer in palm of hand before administering. Do not roll the vaccine sprayer in your hand, as this may dislodge the dose divider clip. May also be thawed in a refrigerator and stored at 35° to 46°F (2° to 8°C) for no more than 60 hours prior to use. **Do not refreeze after thawing.**

Shelf Life After Thawing

The vaccine should be administered shortly after thawing. Vaccine thawed in the refrigerator and stored at 35° to 46°F (2° to 8°C) that is not used within 60 hours must be discarded in an impenetrable sharps container.

Special Instructions

Rotate stock so that the earliest dated material is used first.

NOTE: all materials used for administering live virus vaccines should be burned, boiled, or autoclaved prior to disposal.

* 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) notify the Quality Control office at the vaccine manufacturer; and 3) notify your state health department immunization program if vaccine was publicly purchased vaccine.

MMR: Measles/Mumps/Rubella Vaccine, MR: Measles/Rubella Vaccine, Measles Virus Vaccine, Mumps Virus Vaccine, Rubella Virus Vaccine

Shipping Requirements

Vaccine: Use insulated container. Must be shipped with refrigerant. Maintain 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. If above this temperature, see instructions (*) below. **Do not use warm vaccine.** Refrigerate upon arrival.

Storage Requirements

Vaccine may be stored separately from diluent. Store as follows:

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 virus.

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: Freeze-dried (lyophilized) MMR vaccine may be maintained at freezer temperatures.

Shelf Life

Check expiration date on container or vial.

Instructions for Reconstitution and Use

Reconstitute just before using. Use only the diluent supplied to reconstitute the vaccine. Inject diluent into the vial of lyophilized vaccine and agitate to ensure thorough mixing. Withdraw entire contents into syringe and inject total volume of vaccine subcutaneously.

Shelf Life After Reconstitution, Thawing or Opening

After reconstitution, use immediately or store in a dark place at 35° to 46°F (2° to 8°C). **Discard if not used within 8 hours.**

Special Instructions

Rotate stock so that the earliest dated material is used first.

NOTE: all materials used for administering live virus vaccines should be burned, boiled, or autoclaved prior to disposal.

C

* 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) notify the Quality Control office at the vaccine manufacturer; and 3) notify your state health department immunization program if vaccine was publicly purchased vaccine.

MCV4: Meningococcal Conjugate Vaccine, Groups A, C, Y, W-135

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.

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.**

Shelf Life

Check expiration date on vial or container.

Instructions for Use

Follow manufacturer's directions.

Shelf Life After Opening

The vaccine should be administered shortly after withdrawal from the vial.

Special Instructions

Rotate stock so that the earliest dated material is used first. Vaccine should be injected by the intramuscular route. Do not inject intradermally, subcutaneously, or intravenously.

MPSV4: Meningococcal Polysaccharide Vaccine, Groups A, C, Y, W-135

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.

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 container.

Instructions for Reconstitution and Use

Reconstitute gently. This is a white powder that yields a clear, colorless liquid when reconstituted with 0.6 ml (single-dose vial) or 6 ml (10-dose vial) of sterile distilled water.

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 reconstitution.

Special Instructions

Diluent to be used is sterile, distilled water for injection; diluent for 10-dose vial also contains 0.01% thimerosal. Reconstituted vaccine should be injected subcutaneously. Do not inject intradermally, intramuscularly, or intravenously.

Rotate stock so that the earliest dated material is used first.

* 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) notify the Quality Control office at the vaccine manufacturer; and 3) notify your state health department immunization program if vaccine was publicly purchased vaccine.

PCV: Pneumococcal Conjugate Vaccine (7-Valent)

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.

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 container.

Instructions for Use

Vaccine should appear as a homogenous white suspension after vigorous shaking. The vaccine should be administered intramuscularly only.

Shelf Life After Opening

The vaccine should be administered shortly after withdrawal from the vial.

Special Instructions

This vaccine is a suspension containing adjuvant and should not be used if the particles cannot be resuspended after vigorous shaking.

Rotate stock so that the earliest dated material is used first.

PPV: Pneumococcal Polysaccharide Vaccine (Polyvalent)

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.

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 container.

Instructions for Use

Follow manufacturer's directions.

Shelf Life After Opening

Single-Dose Vials: The vaccine should be administered shortly after withdrawal from the vial.

Multidose Vials: Unused portions of multidose vials may be refrigerated at 35° to 46°F (2° to 8°C) and used until outdated, if not contaminated.

Special Instructions

Do not inject intravenously. Intradermal administration may cause severe local reactions and should be avoided.

Rotate stock so that the earliest dated material is used first.

* 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) notify the Quality Control office at the vaccine manufacturer; and 3) notify your state health department immunization program if vaccine was publicly purchased vaccine.

Varicella (Chickenpox) Vaccine

Shipping Requirements

Vaccine: Use insulated container. Must be shipped with dry ice only, at 4°F (-20°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 4°F (-20°C) or colder until arrival at the healthcare facility. Dry ice should still be present in the shipping container when vaccine is delivered.

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 doors and compartments. Acceptable storage may be achieved in standard household freezers purchased in the last 10 years, and standard household refrigerator/freezers with a separate, sealed freezer compartment. "Dormitory-style" units are not appropriate for the storage of varicella vaccine.

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 container or vial.

Instructions for Reconstitution and Use

Reconstitute just before using. Use only the diluent supplied to reconstitute the vaccine.

Shelf Life After Reconstitution, Thawing or Opening

Protect from light. Discard if not used within **30 minutes** of reconstitution.

Special Instructions

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 1-800-609-4618 for a reevaluation of the product potency before using the vaccine.

Rotate stock so that the earliest dated material is used first.

NOTE: all materials used for administering live virus vaccines should be burned, boiled, or autoclaved prior to disposal.

C

* 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) notify the Quality Control office at the vaccine manufacturer; and 3) notify your state health department immunization program if vaccine was publicly purchased vaccine.

Manufacturer Quality Control Office Telephone Numbers

Manufacturer/Distributor	Telephone Number	Products
sanofi pasteur www.us.aventispasteur.com	800-822-2463	DTaP, DTaP-Hib, DT, Td, TT, Hib, MCV4, MPSV4, Influenza (TIV), IPV
Bayer Biological Products www.bayerbiologicalsusa.bayerhealthcare.com/products.asp	800-288-8371	IGIM, HBIG, TIG
Centers for Disease Control & Prevention Drug Service www.cdc.gov/ncidod/srp/drugs/drug-service.html	404-639-3670	Distributor for Diphtheria antitoxin
Chiron www.chiron.com/products/vaccines/index.html	800-200-4278 (medical information pharmacist) 800-244-7668 (customer support)	Influenza (TIV)
GlaxoSmithKline www.gsk.com/products/vaccines.jsp	866-475-8222 (customer support) 888-825-5249 (customer support)	DTaP, DTaP-HepB-IPV, HepA, HepB, HepA-HepB
Massachusetts Biological Labs	617-983-6400	Td, TT, IGIM, VZIG
MedImmune, Inc. www.medimmune.com	877-358-6478 (LAIV customer support) 877-633-4411 (general customer support)	Influenza (LAIV)
Merck www.merck.com	800-609-4618 (customer support) 800-672-6372 (customer support)	Hib, Hib-HepB, PPV23, HepA, HepB, MMR, Measles, Mumps, Rubella, Varicella
Nabi Biopharmaceuticals www.nabi.com	800-635-1766	HBIG
Wyeth www.wyeth.com	800-999-9384 (storage) 800-934-5556 (customer support) 800-666-7248 (customer support)	Hib, PCV7

July 2004

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.
____	____	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.
____	____	0.	We always keep a thermometer in the refrigerator.
____	____	1.	The temperature in the refrigerator is maintained at 35–46°F (2–8°C).
____	____	2.	We keep extra containers of water in the refrigerator to help maintain cold temperatures.
____	____	3.	We always keep a thermometer in the freezer.
____	____	4.	The temperature in the freezer is maintained at +5°F (-15°C) or colder.
____	____	5.	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.
____	____	7.	We have a "Do Not Unplug" sign next to the refrigerator's electrical outlet.
____	____	8.	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.
____	____	9.	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!

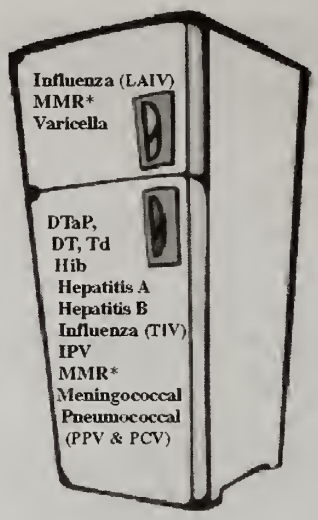
www.immunize.org/catg.d/p3035chk.pdf • Item #P3035 (8/01)

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.

C

*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

www.immunize.org/catg.d/p3048.pdf • Item #P3048 (11/03)

WARNING

Do not unplug the refrigerator/
freezer or break circuit.
Expensive vaccine in storage.

In event of electrical problem, immediately contact:

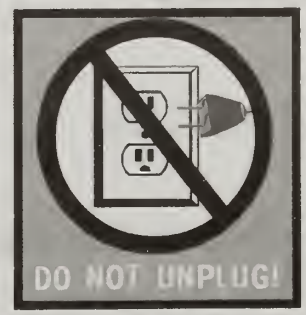
WARNING

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.



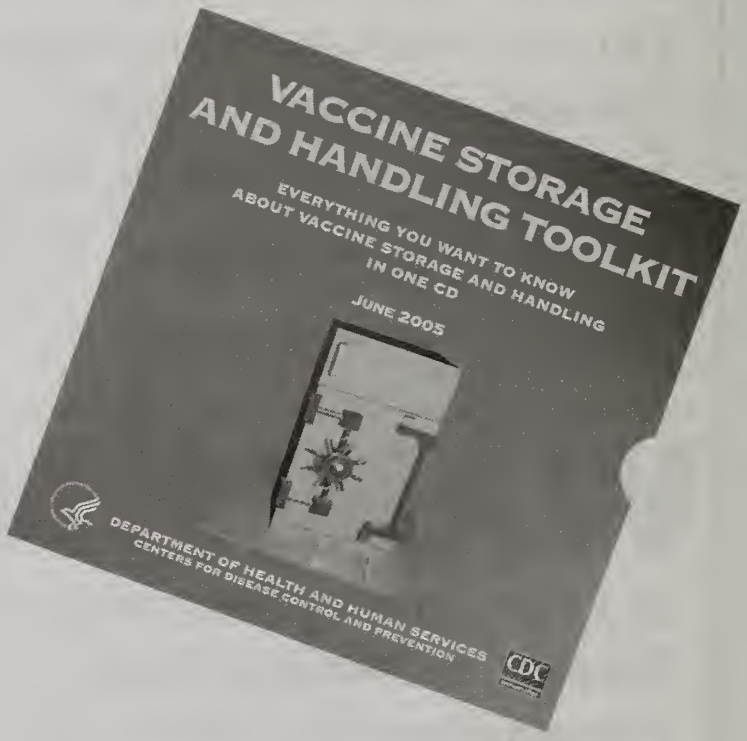
In event of electrical problem, immediately contact:

New from CDC:

Vaccine Storage and Handling Toolkit

Everything you want to know about vaccine storage and handling in one place!

- Storage & handling guidelines
- Two videos
- Interactive game
- Forms
- Posters
- Checklists
- Contact information



Online at www2a.cdc.gov.nip/isd/shtoolkit/splash.html

or

Order ***CD-ROM*** from www.cdc.gov/nip/publications

APPENDIX D
Vaccine Administration

Appendix D

Vaccine Administration

Appropriate vaccine administration is critical to vaccine effectiveness. The recommended site, route and dosage for each vaccine is 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, Centers for Disease Control and Prevention's (CDC) 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 and/or adults (refer to "Skills Checklist for Pediatric Immunization" – page G13).

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 (refer to "Be there for your child during shots" – page G15). Parents/guardians who elect not to directly participate during vaccine administration can wait in a nearby area.

  - **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 included in Appendix A

  - **Vaccine Safety & Risk Communication** - Parents/guardians and patients are exposed through the media to information about vaccines, some of which is inaccurate or misleading. Health-care 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 (refer to Chapter 17 and Appendix F).

  - **Atraumatic Care** - Vaccine safety issues and the need for multiple injections have increased the concerns and anxiety associated with immunizations. Health-care 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 health-care 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 G17).

- **Pain Control** - Pain is a subjective phenomenon influenced by multiple factors, including an individual's age, anxiety level, previous health-care experiences, and culture. Consideration for these factors is important as the provider develops a planned approach to management of injection pain (see page G15).

  ✓ **Topical Anesthetics** or a vapocoolant spray may be prescribed pre-vaccination 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 (refer to "After the shots. . ." in Appendix A).

  ✓ **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 pages G15-16.

  ✓ **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 widely evaluated.

- **Infection Control** - Health-care 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, etc.

  - **Gloving** - Gloves are not mandatory for vaccine administration unless there is potential for exposure to blood or body fluids or the provider has open lesions on the hands. It is important to remember that gloves cannot prevent needle stick injuries.

  - **Needle Stick Injuries** should be reported immediately to the site supervisor with appropriate care and follow-up given as directed by state/local guidelines.

  - **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 needle sticks 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 and sharps with enginecred sharps injury protection (SESIP) are available, 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 product evaluation and selection. Prior to use in the clinical area, staff should receive training with the device.

  - **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, and viscosity of the vaccine (See Subcutaneous & Intramuscular Injections below). Typically vaccines are not highly viscous, and therefore, a fine gauge needle can be used (22-25 gauge).

  - **Needle-free Injection** - A new generation of needle-free vaccine delivery devices has been developed in an effort to decrease the risks of needle stick injuries to health-care workers and to prevent improper reuse of syringes and needles. For more information on needle-free injection technology consult the CDC website, www.cdc.gov/nip/dev/jetinject.htm.

- **Inspecting Vaccine** - Each vaccine vial should be carefully inspected for damage or contamination 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. Vaccine past its expiration date 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; only the specific diluent supplied for the vaccine should be used. Once the vaccine vial is uncapped, clean the rubber stopper of the vial with an alcohol wipe and allow to dry. Inject the entire content of the diluent vial into the vial of lyophilized vaccine and agitate to ensure thorough mixing. Once reconstituted, the vaccine must be 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 steps for filling the syringe.

- **Filling the Syringe** -

  - For vaccines that do not require reconstitution, uncap the vaccine vial, clean the rubber stopper of the vial with an alcohol wipe and allow to dry.

  - If possible, tighten the needle on the syringe.

  - Pull back on the plunger to fill the syringe with an amount of air equal to the amount of vaccine to be withdrawn.

  - Remove the needle guard and place the guard where it will not become contaminated.

  - With the vial upright, insert the needle directly into the center of the rubber stopper.

- Inject the air into the vial, keeping the bevel of the needle above the level of the vaccine to avoid producing air bubbles in the vaccine. The injected air will create positive pressure in the vial and allow removal of the vaccine without creating a vacuum.

- Invert the vial and withdraw the vaccine keeping the bevel of the needle within the solution to avoid drawing air into the syringe. For single dose vials, withdraw the entire vial contents. For multidose vials, withdraw the desired vaccine dose.

- Remove the vial and expel any air bubbles or excess air from the syringe by gently tapping the side of the syringe and advancing the plunger. Do not expel any of the vaccine.

- Recap the needle. Since the needle has not been injected into the patient, recapping at this point is allowable.

■ **Prefilling Syringes** - The National Immunization Program strongly discourages filling syringes in advance because of the increased risks for administration errors. Once in the syringe, it is difficult to tell which vaccine is which. 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 individuals should draw up and prepare any medications they will administer. An alternative to the practice of 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.

  However, if you have a reason to reconstitute more than one dose of vaccine, perhaps for a large influenza clinic, you should only prefill a few syringes at a time, which you can administer while someone else is prefilling a few syringes they will administer. Any syringes left at the end of the clinic day *should be discarded.*

  Under NO CIRCUMSTANCES should MMR or varicella vaccine ever be reconstituted and drawn prior to the immediate need for the vaccines. These live virus vaccines are unstable and begin to deteriorate as soon as they are reconstituted with diluent.

■ **Labeling** - Once vaccines are drawn up, filled syringes should be identifiable in terms of the vaccine or antigen(s) in the syringe(s). 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). Some providers may choose to include the lot number and date of filling on the identification.

Administration

- **Route** - Administering a vaccine by the recommended route is imperative. Delivering the vaccine into the appropriate tissue promotes optimal vaccine efficacy and diminishes the risk of severe local adverse reactions.

Administering Vaccines: Dose, Route, Site, and Needle Size

Vaccines	Dose	Route	Site	Needle Size
Diphtheria, Tetanus, Pertussis (DTaP, DT, Td)	0.5 mL	IM	**Vastus lateralis:** for infants (& toddlers lacking adequate deltoid mass); **Deltoid:** for toddlers, children & adults	22–25g, 1–2"
***Haemophilus influenzae* type b (Hib)**	0.5 mL	IM	**Vastus lateralis:** for infants (& toddlers lacking adequate deltoid mass); **Deltoid:** for toddlers & children	22–25g, 1–2"
Hepatitis A (HepA)	≤18 yrs.: 0.5 mL ≥19 yrs.: 1.0 mL	IM	**Vastus lateralis:** for infants (& toddlers lacking adequate deltoid mass); **Deltoid:** for toddlers, children & adults	22–25g, 1–2"
Hepatitis B (HepB)	≤19 yrs.: 0.5 mL* ≥20 yrs.: 1.0 mL	IM	**Vastus lateralis:** for infants (& toddlers lacking adequate deltoid mass); **Deltoid:** for toddlers, children & adults	22–25g, 1–2"
Influenza, live attenuated (LAIV)	0.5 mL	Intranasal spray	Administer 0.25 mL dose into each nostril while patient is in an upright position	NA
Influenza, trivalent inactivated (TIV)	6-35 mos: 0.25 mL ≥3 yrs.: 0.5 mL	IM	**Vastus lateralis:** for infants (& toddlers lacking adequate deltoid mass); **Deltoid:** for toddlers, children & adults	22–25g, 1–2"
Measles, mumps, rubella (MMR)	0.5 mL	SC	**Anterolateral fat of thigh:** for young children **Posterolateral fat of upper arm:** for children & adults	23–25g, 5/8"
Meningococcal (Men)	0.5 mL	SC	**Anterolateral fat of thigh:** for young children **Posterolateral fat of upper arm:** for children & adults	23–25g, 5/8"
Pneumococcal conjugate (PCV)	0.5 mL	IM	**Vastus lateralis:** for infants (& toddlers lacking adequate deltoid mass); **Deltoid:** for toddlers & children	22–25g, 1–2"
Pneumococcal polysaccharide (PPV)	0.5 mL	IM	**Deltoid**	22–25g, 1–2"
		SC	**Anterolateral fat of thigh:** for young children **Posterolateral fat of upper arm:** for children & adults	23–25g, 5/8"
Polio, inactivated (IPV)	0.5 mL	IM	**Vastus lateralis:** for infants (& toddlers lacking adequate deltoid mass); **Deltoid:** for toddlers, children & adults	22–25g, 1–2"
		SC	**Anterolateral fat of thigh:** for infants & young children **Posterolateral fat of upper arm:** for children & adults	23–25g, 5/8"
Varicella (Var)	0.5 mL	SC	**Anterolateral fat of thigh:** for young children **Posterolateral fat of upper arm:** for children & adults	23–25g, 5/8"

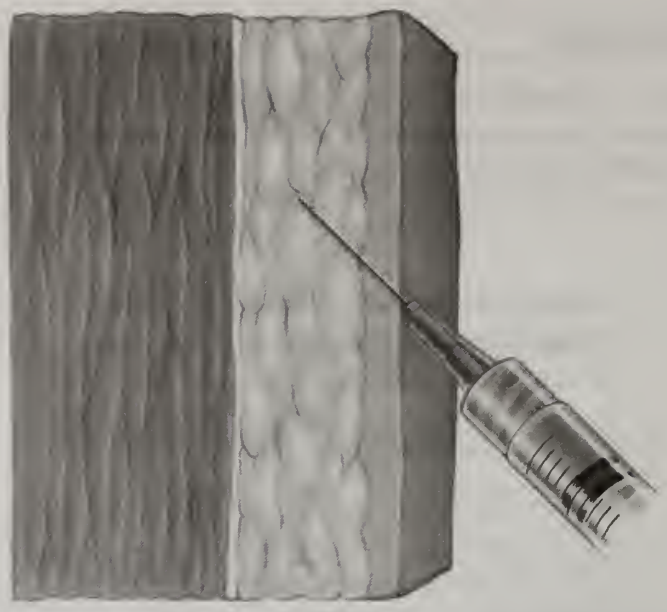
*Persons 11 through 15 years of age may be given Recombivax HB® (Merck) 1.0 mL (adult formulation) on a 2-dose schedule

Combination Vaccines

DTaP+HepB+IPV (Pediarix™) **DTaP+Hib (Trihibit™)** **Hib+HepB (Comvax™)**	0.5 mL	IM	**Vastus lateralis:** for infants (& toddlers lacking adequate deltoid mass); **Deltoid:** for toddlers & children	22–25g, 1–2"
HepA+HepB (Twinrix®)	≥18 yrs.: 1.0 mL	IM	**Deltoid**	22–25g, 1–2"

Please note: Always refer to the package insert included with each biologic for complete vaccine administration information. The Advisory Committee on Immunization Practices (ACIP) statement for the particular vaccine should be reviewed as well.

- **Subcutaneous** (SC) injections are administered into the fatty tissue found below the dermis and above muscle tissue.



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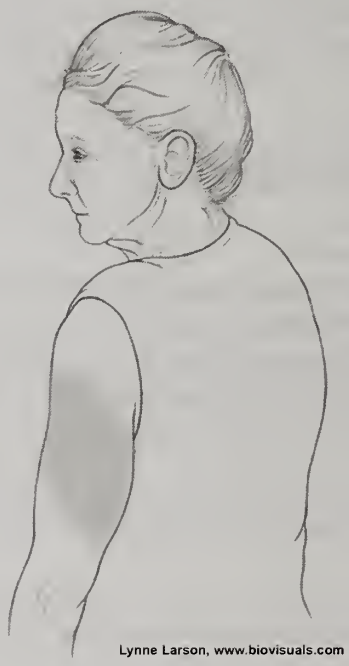
- **Site** - SC tissue can be found all over the body. The usual SC sites for vaccine administration are the thigh and the upper outer triceps of the arm. If necessary, the upper outer triceps area can be used to administer SC injections to infants.



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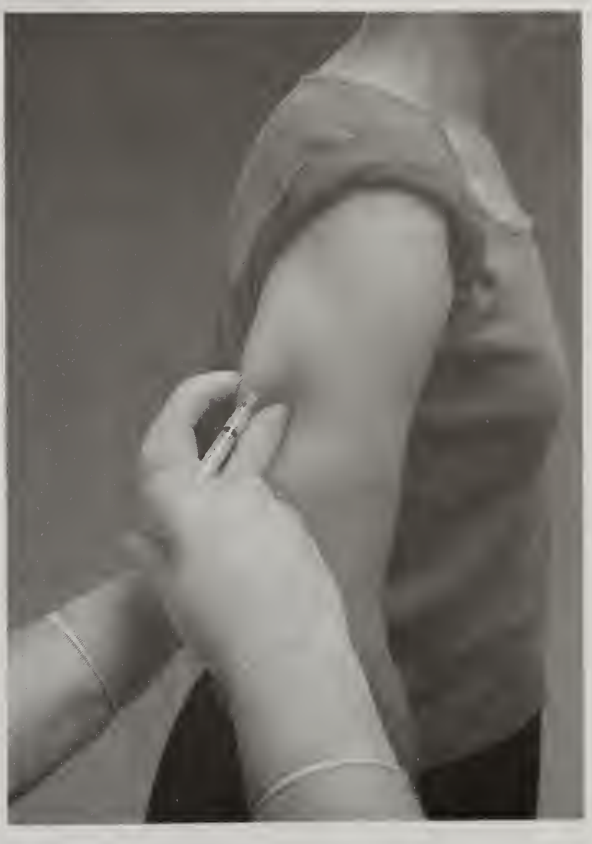
- **Needle Gauge & Length** - 5/8-inch, 23- to 25-gauge needle

- **Technique**

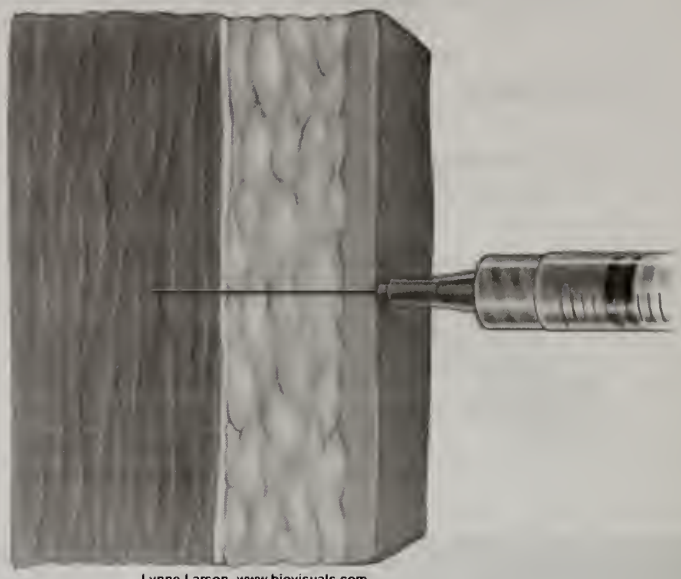
  ✓ Following appropriate site assessment/selection, prep the injection site with an alcohol wipe. Using a circular motion, wipe from the center out and allow to dry.

  ✓ To avoid reaching the muscle, the fatty tissue is pinched up, the needle is inserted at a 45 degree angle and the vaccine is injected into the tissue.

  ✓ Withdraw the needle and apply light pressure to the injection site for several seconds with a dry cotton ball/gauze.



- **Intramuscular** (IM) injections are administered into muscle tissue below the dermis and SC tissue.



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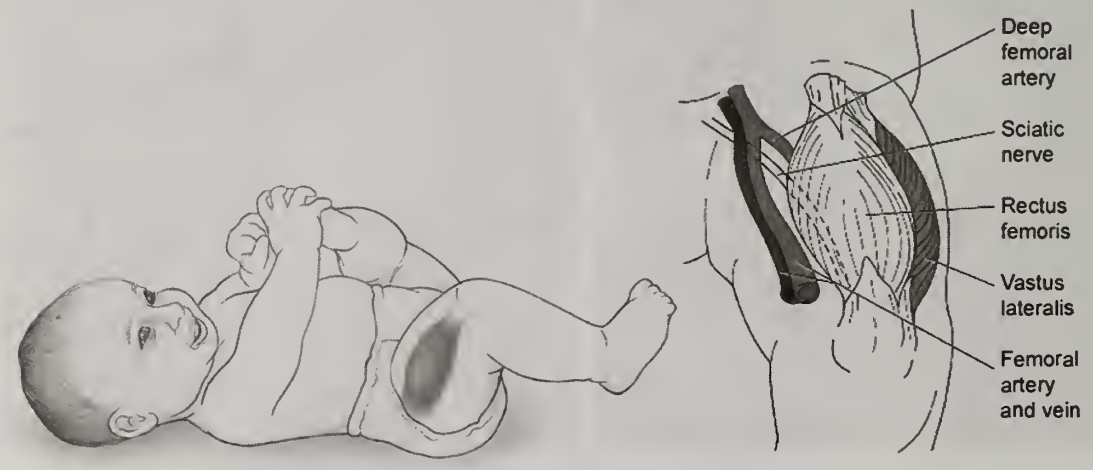
- **Site** - Although there are several IM injection sites on the body, the recommended IM sites for vaccine administration are the vastus lateralis muscle (anterolateral thigh) and the deltoid muscle (upper arm). The site depends on the age of the individual and the degree of muscle development.



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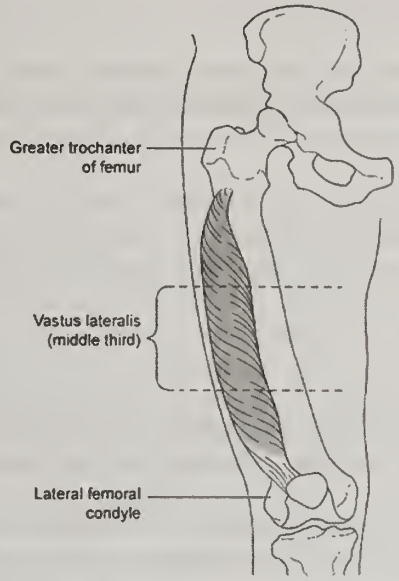
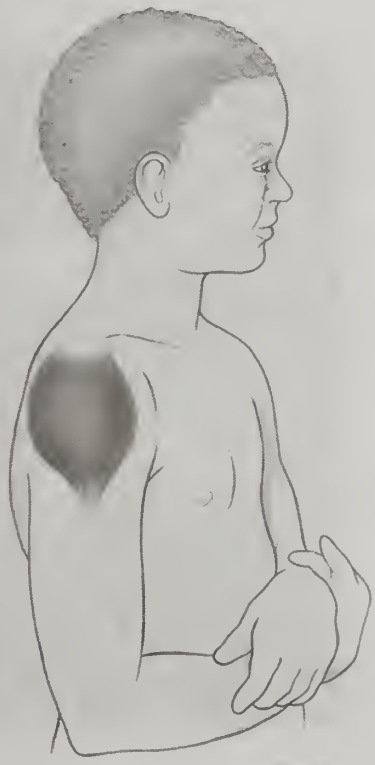
The vastus lateralis muscle of the upper thigh used for intramuscular injections.



The vastus lateralis site of the right thigh, used for an intramuscular injection.

The deltoid muscle site is most commonly used in older children and adults. The deltoid muscle can be used in toddlers if the muscle mass is adequate. The buttock should never be used to administer vaccines.



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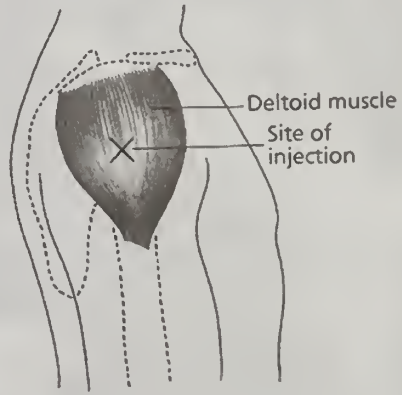


- **Needle Gauge** - 22- to 25-gauge needle

  - **Needle Length** - The needle length must be adequate to reach the muscle and is based on the size of the individual. Following are the typical lengths for various ages.

    Infant - 7/8- to 1-inch

    Toddler & older children - 7/8- to 1 1/4-inch

    Adults - 1- to 1 ½-inch

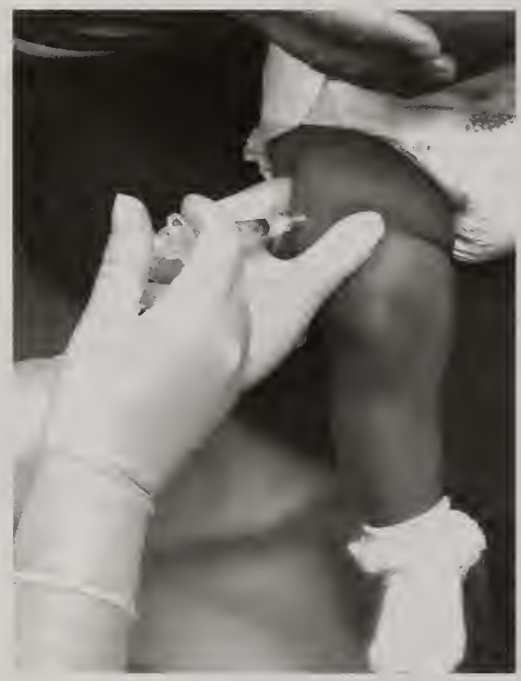
  - **Technique** -

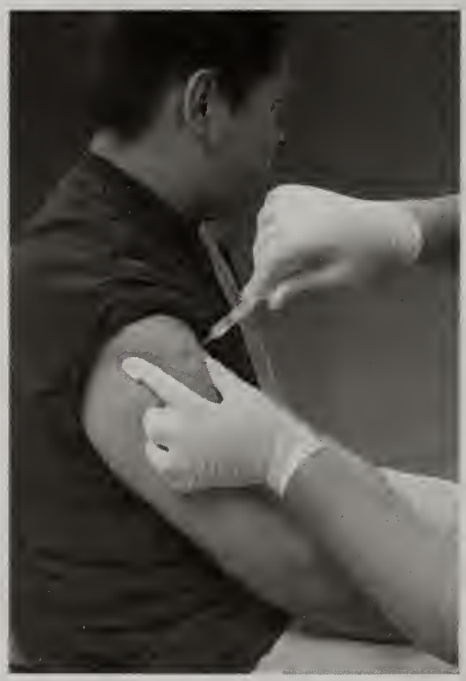
    ✓ Following appropriate site assessment/selection, prep the injection site with an alcohol wipe. Using a circular motion, wipe from the center out and allow to dry.

    ✓ To avoid injection into SC tissue, the skin of the selected vaccine administration site can be spread 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 degree 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/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, there is no research data documented to support the need for this procedure. If blood appears following aspiration, the needle should be withdrawn, a new site selected and the entire administration process restarted.

- **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 0.5 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 SC vaccine into the same limb, if necessary, is acceptable since a different tissue site is involved.

- **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 2002; 51 (RR-2), for specific guidance.

Special Situations

- **Bleeding Disorders** - Individuals with a bleeding disorder or who are receiving anticoagulation 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 two 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.

- **Limited Sites** - Sometimes vaccination sites may be limited in an individual because of amputation, injury, orthopedic device or cast, etc. It may be necessary to consult the patient's primary health-care provider to develop an individualized immunization schedule.

- **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 may consider having the patient sit during injection(s). A syncopal or vasovagal response is not an allergic reaction, however, 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 detailed information on medical management, refer to the ACIP General Recommendations on Immunization and AAP Red Book. Although both fainting and allergic reactions are rare, some experts suggest observing patients for 15-20 minutes following vaccine administration.

Documentation - All vaccine administration should be fully documented in the patient's permanent medical record to 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 either in the lower left or lower right corner 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 vaccine registries. 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, including a training video, posters and a skills checklist. Ordering information is available on the Immunization Action Coalition (IAC) website, http://www.immunize.org/iztech/index.htm.

Skills Checklist for Pediatric Immunization

Goal: To assure clinical staff has the skills and competencies needed for safe, effective and caring administration of pediatric immunizations.

Purpose: The Skills Checklist can be used for self-assessment or for annual performance reviews by physician or supervisor. It also can be used for new employees, to identify what they will need in orientation and what knowledge or skills they should attain during their probationary period.

Instructions: Prior to annual review, staff should score themselves (self-assessment) on the items below. After their self-assessment, the medical director or supervisor should observe their skills and techniques with several patients. Score by checking in the appropriate column. Discuss in private any scoring differences and recommend a plan of action for any scores of **"Needs Review"**.

Scoring:

Needs Review: Needs improvement. Institute a corrective plan of action to develop appropriate skills level. Review again in 30 days, followed by 3 months review if needed.
Meets or Exceeds: Demonstrates competencies and skills required for safe, effective and caring pediatric immunization administration. File in personnel folder. Review again at end of probationary period and annually thereafter.

		Self Assessment		Supervisor Review		
Competency	**Clinical Skills, Techniques, and Procedures**	**Needs Review**	**Meets or Exceeds**	**Needs Review**	**Meets or Exceeds**	**Plan of Action***
A. Parent Education	1. Welcomes child and family, establishes rapport, and answers parents 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 parents to help make them feel comfortable and informed about the procedure.					
	4. Verifies parents received the Vaccine Information Statements for all vaccines the child is to receive 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 parent, 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.					
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, Hib, HepA, HepB, Pneumo Conj); 5/8" for SC (MMR, Var); IPV depends on route to be used.					
	4. Reconstitutes and/or draws vaccine into syringe correctly.					
	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: Needs Review	Self Assessment: Meets or Exceeds	Supervisor Review: Needs Review	Supervisor Review: 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. [Intramuscular (IM) for DTaP, Hib, HepA, HepB, Pneumo Conj; Subcutaneous (SC) for MMR, Var; Either SC or IM for IPV].					
	4. Positions and restrains the patient; locates anatomic landmarks specific for IM or SC.					
	5. Preps the skin, cleaning the site and a 2" to 3" circle around it. Allows alcohol to dry.					
	6. Inserts the needle at the appropriate angle to skin (45° for SC or 90° for IM); if office policy, aspirate.					
	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 sterile pad.					
	9. Properly disposes of needle and syringe in sharps container. Properly disposes of live vaccine vial.					
	10. Understands the need to report any needlestick injury and to maintain a sharps injury log.					
	11. 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.					
	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 parents' record of their child's immunizations and reminds them to bring it to each visit.					

***Plan of Action:** Might include: Review manual or textbook section on injections; review package insert; review office protocols or other references; watch video on administration techniques or vaccine handling; observe proper technique, practice injections; read Vaccine Information Statements; mentor with someone who has these skills; do role playing with other staff; attend an update, skills training or refresher course; attend cultural competency training; etc. Plan of action must include a deadline and date for a 30-day and a 3-month follow-up review.

Performance Review Acknowledgement:

Employee _____ Date _____ Plan of Action Time Frame _____

Supervisor _____ Date _____ Date for Follow-up Review _____

IMMUNIZATION TECHNIQUES
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IMM-694 (12/11/00)

Age, Body Mass, Needle Length, and Site

Newborns, Infants, Toddlers, and Children (Through 10 Years)		
Age	**Needle Length**	**Injection Site**
Newborn* (Premature or Term)	5/8" (16mm)	Anterolateral Thigh
Infant 1-12 months	7/8" - 1" (22-25mm)	Anterolateral Thigh
Child or Toddler 1-10 years	7/8" - 1 1/4" (22-32mm)	Deltoid Muscle of the Arm
	1 - 1 1/4" (25-32mm)	Anterolateral Thigh
Pre-Adolescents, Adolescents, and Adults (11 Years and Older)		
Sex/Weight	**Needle Length** (minimum)	**Injection Site**
Female ≤ 90 kg (200 lbs)	1" (25mm)	Deltoid Muscle of the Arm
Male ≤118 kg (260 lbs)		
Female > 90 kg (200 lbs)	1½" (38mm)	
Male >118 kg (260 lbs)		

*Newborn = First 28 days of life

Adapted from AAP Red Book, Poland G, JAMA, 1977, and 2002 ACIP General Recommendations

For 8 1/2" x 11" copies, enlarge to 155%

Immunization Site Map

Suggested sites for infant immunizations:

RD: _____

RT: _____

RT: _____

LD: _____

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

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IMM-718 (5/01)

Immunization Site Map

Suggested sites for toddler immunizations:

RD: _____

RT: _____

RT: _____

LD: _____

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)

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

dhs
IMM 720 (12/01)

APPENDIX E
Vaccine Information Statements

Appendix E

It's federal law!

You must give your patients current Vaccine Information Statements (VISs)

***A vaccine complication** in Florida highlights the importance of distributing the most recent VIS to your patients. In 1997, a 3-month-old boy developed vaccine-associated paralytic poliomyelitis (VAPP) following a first dose of OPV. The boy's parents reported that their physician furnished them with the 1994 polio VIS at the time of vaccination. The polio VIS had been revised in 1997 to reflect the ACIP preference for sequential use of inactivated polio vaccine (IPV) followed by live polio vaccine (OPV), making the 1994 polio statement that was given to the parent outdated. Note: the most current polio VIS carries the date of 1/1/00.*

This article was originally written by Neal A. Halsey, MD, Director, Institute for Vaccine Safety, Johns Hopkins Bloomberg School of Public Health and was updated by the Immunization Action Coalition in December 2005.

As readers of *NEEDLE TIPS* understand, the risks of serious consequences following vaccines 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 such as the one in the Florida case 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 vaccinees (or the parents/legal guardians 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 health care 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 vaccinee or the minor child's parent or legal representative about the risks and benefits of each vaccine. The VISs are not meant to replace interactions with healthcare providers who should answer questions and address concerns that the vaccinee or the parent/legal representative may have.

"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 health care providers are required by law to provide prior to the administration of vaccines."

Walter A. Orenstein, MD, Past Director National Immunization Program, CDC

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 B, *Haemophilus influenzae* type b (Hib), varicella (chickenpox), or pneumococcal conjugate vaccine, the provider is required by the National Childhood Vaccine Injury Act (NCVIA) to provide a copy of the VIS to either the adult vaccinee or to the child's parent/legal representative.

VISs are also available for influenza, pneumococcal polysaccharide, hepatitis A, meningococcal, yellow fever, rabies, anthrax, and typhoid vaccines, and their use is recommended but not required by federal law. (EDITOR'S NOTE: Use of the VISs for hepatitis A, influenza, and meningococcal vaccines will become mandatory later in 2005. These vaccines are, or soon will be, covered by the NCVIA.)

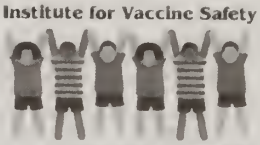
State or local health departments or individual providers may place identifiers on the VISs but any other changes must be approved by the Director of CDC's National Immunization Program.

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, a date which appears on the bottom of the VIS. As the Florida case above illustrates, it is imperative that you have the most current VIS.

Institute for Vaccine Safety



Johns Hopkins University

The Institute for Vaccine Safety is committed to investigating vaccine safety issues and providing timely and objective information on vaccine safety to health care providers, journalists, and parents. Visit their website at www.vaccinesafety.edu

Most current versions of VISs

As of December 2005, the most recent versions of the VISs are as follows:

DTaP/DT/DTP	7/30/01	PCV	9/30/02
hepatitis A	8/4/04	PPV	7/29/97
hepatitis B	7/11/01	polio	1/1/00
Hib	12/16/98	rabies	11/4/03
influenza (LAIV)	10/20/05	Td	6/10/94
influenza (TIV)	10/20/05	Tdap	9/22/05
Japan. enceph.	5/11/05	typhoid	5/19/04
meningococcal	10/7/05	varicella	12/16/98
MMR	1/15/03	yellow fever	11/9/04

How to get VISs

VISs are available by calling your state or local health department. They also can be downloaded from the Immunization Action Coalition's website at www.immunize.org/vis or CDC's website at www.cdc.gov/nip/publications/vis

Foreign language versions of VISs are not officially available from the CDC. However, several state health departments have arranged for their translations. These versions do not require CDC approval. You can find more than 30 languages on the Immunization Action Coalition's website at www.immunize.org/vis or call your state health department. ♦

To obtain a complete set of current VISs, call your state health department or visit www.immunize.org/vis

www.immunize.org/catg.d/p2027law.pdf • Item #P2027 (12/05)

Instructions for the Use of
Vaccine Information Statements

Required Use

1. Provide 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** any vaccine containing diphtheria, tetanus, pertussis, measles, mumps, rubella, polio, hepatitis B, *Haemophilus influenzae* type b (Hib), trivalent influenza (use of influenza VIS required effective January 1, 2006), pneumococcal conjugate, or varicella (chickenpox) vaccine 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 the Centers for Disease Control and Prevention's website at http://www.cdc.gov/nip/publications/VIS. Copies are available in English and in other languages.

Current Editions of VISs

Diphtheria, Tetanus, Pertussis (DTaP/DT): 7/30/01
Haemophilus influenzae type b: 12/16/98
Hepatitis B: 7/11/01
Inactivated Influenza: 10/20/05
Live, Intranasal Influenza: 10/20/05
Measles, Mumps, Rubella (MMR): 1/15/03
Pneumococcal conjugate: 9/30/02
Polio: 1/1/00
Tetanus Diphtheria (Td): 6/10/94
Varicella (chickenpox): 12/16/98

Reference 42 U.S.C. §300aa-26

11/4/2005

How to Get Vaccine Information Statements

1. **The Internet.** All current VISs are available on the internet at two websites:
   - The National Immunization Program (www.cdc.gov/nip/publications/vis/default.htm)
   - The Immunization Action Coalition (www.immunize.org/vis/index.htm)

   VISs from these sites can be downloaded as pdf files and printed. You can also order single hard copies of the VISs using NIP's Online Order Form (at www.cdc.gov/nip/publications).

2. **State Health Department.** CDC sends each state health departments immunization program camerarady copies when a new VIS is published. The immunization program in turn provides copies to providers within the state.

A set of 7 **Videotapes** of VISs (MMR, DTP, Polio, Hepatitis B, Hib, Varicella, and Pneumococcal Conjugate) is available in English and Spanish from Michigan State University Extension. Tapes run approximately 59 minutes each, and a set costs $25. For information, call (517) 432-8204.

Audio files for most VISs can be downloaded from the National Immunization Program's VIS webpage (www.cdc.gov/nip/publications/vis/default.htm).

Text versions of the VISs can also be accessed from the National Immunization Program's VIS webpage. These files are compatible with screen-reader devices.

VIS **Translations** are available in more than 30 languages from the Immunization Action Coalition's website at www.immunize.org/vis/index.htm.

Arabic	French	Korean	Samoan
Armenian	German	Laotian	Serbo-Croatian
Bosnian	Haitian	Marshallese	Somali
Burmese	Hindi	Polish	Spanish
Cambodian	Hmong	Portuguese	Tagalog
Chinese	Ilokano	Punjabi	Thai
Croatian	Italian	Romanian	Turkish
Farsi	Japanese	Russian	Vietnamese

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 technical ly 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 deter mine 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 the NIP 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 the National Immunization Program's VIS webpage will always be current, regardless of the edition date.

8. **Sometimes a VIS will contain a recommendation 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. Package inserts generally tend to include 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 (e.g., "individual") and short words that are not (e.g., "spiv"). 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 reveals about a 10th grade reading level, but this should be taken with the caveats in the preceding paragraph.

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 (some not native English speakers) in 1998, and the participants overwhelmingly rated them easy to read and understand.

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). As of November 2005, these VISs are DTaP, Td, MMR, Polio, Hepatitis B, Haemophilus influenzae type b (Hib), Varicella, Pneumococcal conjugate and Influenza vaccine. Final VISs for Hepatitis A and Tdap will be available soon, and meningococcal conjugate vaccine will soon be covered by the NVCIA.

VISs are available for all vaccines licensed in the United States (except BCG). Their use is strongly encouraged, whether it is 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 Immunization Program.

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.

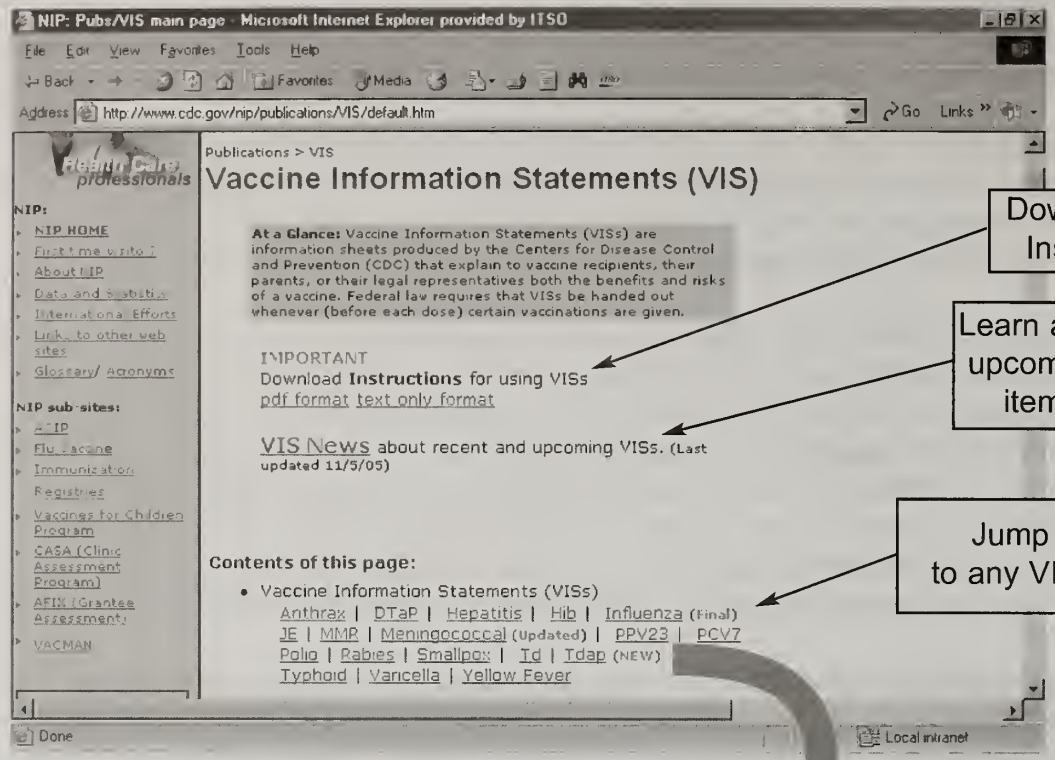
The program must maintain the original consent signature and any additional dose veto statements in the patient's medical record. A record must be kept of the dates prior to additional doses that the VIS was mailed, or sent home with the adolescent.

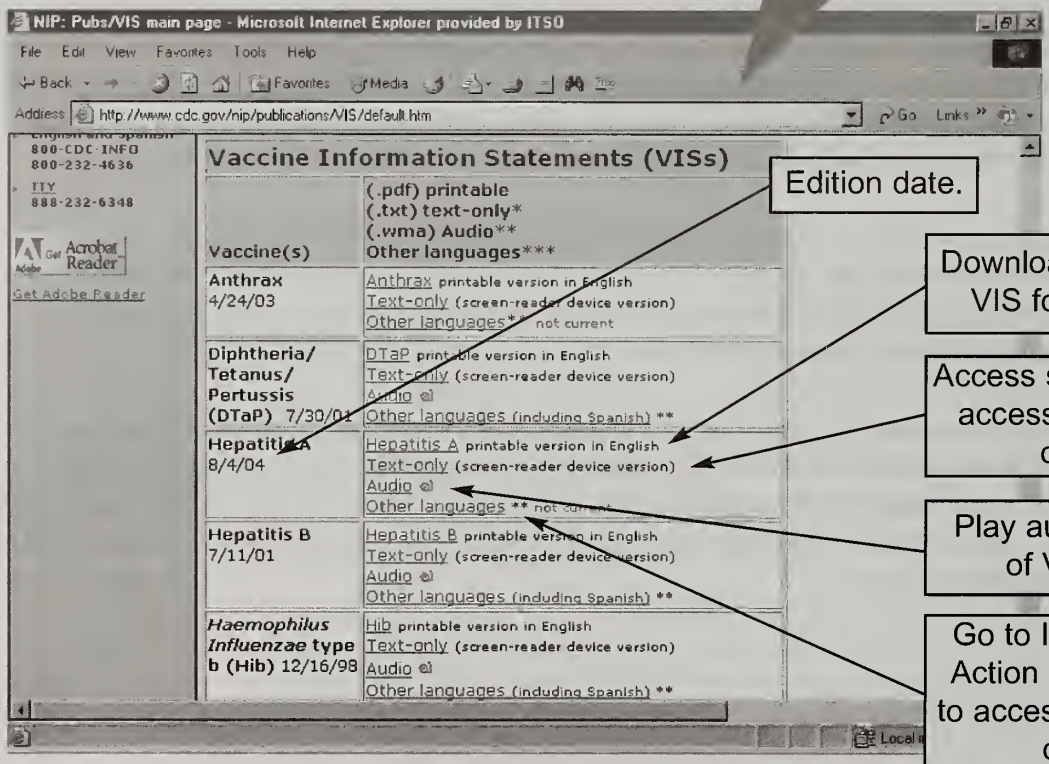
Prior to administration of each additional dose, the provider should ask the adolescent whether he/she experienced any significant adverse events following receipt of earlier doses. If yes, the provider should consider consulting the parent or delaying the vaccination. The adolescent's response to questions about adverse reactions to previous doses should be kept in the medical record.

Appendix E

CDC's Vaccine Information Statement Webpage

http://www.cdc.gov/nip/publications/VIS/default.htm





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APPENDIX F
Vaccine Safety

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 (F2), 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 F6) 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 http://www.fda.gov/cber/vaers/vaers.htm
- The Centers for Disease Control and Prevention Web site at http://www.cdc.gov/nip/

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).

Table of Reportable Events Following Vaccination (RET)

Vaccine/Toxoid	Event	Interval from Vaccination
Tetanus in any combination; DTaP, DTP, DTP-Hib, DT, Td, or TT)	A. Anaphylaxis or anaphylactic shock	7 days
	B. Brachial neuritis	28 days
	C. Any sequelae (including death) of above events	Not applicable
	D. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert
Pertussis in any combination; DTaP, DTP, DTP-HiB, P	A. Anaphylaxis or anaphylactic shock	7 days
	B. Encephalopathy (or encephalitis)	7 days
	C. Any sequelae (including death) of above events	Not applicable
	D. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert
Measles, mumps and rubella in any combination; MMR, MR, M, or R	A. Anaphylaxis or anaphylactic shock	7 days
	B. Encephalopathy (or encephalitis)	15 days
	C. Any sequelae (including death) of above events	Not applicable
	D. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert
Rubella in any combination; MMR, MR, R	A. Chronic arthritis	42 days
	B. Any sequelae (including death) of above event	Not applicable
	C. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert
Measles in any combination; MMR, MR, M	A. Thrombocytopenic purpura	7-30 days
	B. Vaccine-strain measles viral infection in an immunodeficient recipient	6 months
	C. Any sequelae (including death) of above event	Not applicable
	D. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert

Oral **Polio** (OPV)	A. Paralytic polio	30 days/ 6 months
	B. Vaccine-strain polio viral infection	30 days/ 6 months
	C. Any sequelae (including death) of above events	Not applicable
	D. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert
Inactivated **Polio** (IPV)	A. Anaphylaxis or anaphylactic shock	7 days
	B. Any sequelae (including death) of the above event	Not applicable
	C. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert
Hepatitis B	A. Anaphylaxis or anaphylactic shock	7 days
	B. Any sequelae (including death) of the above event	Not applicable
	C. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert
Haemophilus 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	30 days
	B. Any sequela (including death) of the above event	Not applicable
	C. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert
Pneumococcal conjugate	A. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert

*Effective date: August 26,2002.
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:

1. 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
2. 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.
3. 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.

Early-onset Hib disease is defined as invasive bacterial illness associated with the presence of *Haemophilus influenzae* b (Hib) organism on culture of normally sterile body fluids or tissue, or clinical findings consistent with the diagnosis of epiglottitis. Hib pneumonia qualifies as invasive Hib disease when radiographic findings consistent with the diagnosis of pneumonitis are accompanied by a blood culture positive for the Hib organism. Otitis media, in the absence of the above findings, does not qualify as invasive bacterial disease. A child is considered to have suffered an adverse event only if the vaccine was the first Hib immunization received by the child.

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.org 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)

F

"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.

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 - F9).

The Claims Process

An individual claiming a vaccine-related injury or death files a petition for compensation with the Court, and is 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/osp/vicp 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/osp/vicp)

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]	A No condition specified for compensation	Not applicable

[a] Effective date: July 1, 2005

[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. See *News* on the VICP website for more information (www.hrsa.gov/osp.vicp).

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 l 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 infec- tion, 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- con- sider 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 movements 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 dys func tion 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 infection** 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

Appendix G

Reported Cases and Deaths from Vaccine Preventable Diseases, United States, 1950-2003

	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

Appendix G

	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	NA	231	NA	7	NA	1

	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

	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	NA	231	NA	7	NA	1

	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

	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	NA	7,526	NA	2,013	NA	20,948	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 2003, 32 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 2003, varicella cases were reported from 21 states, the District of Columbia, Guam, Puerto Rico and American Samoa.

Sources:
Final totals for 2003: *MMWR* 2004;53(40):688-96.

Reportable diseases (1971-2002): Summary of Notifiable Diseases, United States, 2002. *MMWR* 2004;51(53):74-8.

Reportable disease (1950-1970): Earlier editions of Summary of Notifiable Diseases, published annually in *MMWR*.

Deaths: National Center for Health Statistics Mortality Report for respective years.

8 Dec 2004

Impact of Vaccines in the 20th Century

Disease	20th Century Annual Morbidity	2003 Total	% Decrease
Smallpox	48,164	0	100
Diphtheria	175,885	1	>99.9
Pertussis	147,271	11,647	92.1
Tetanus	1,314	20	98.5
Polio (paralytic)	16,316	0	100
Measles	503,282	56	>99.9
Mumps	152,209	231	99.9
Rubella	47,745	7	>99.9
Congenital rubella	823	1	99.8
Haemophilus influenzae (<5 yrs)	20,000 (est.)	259 (serotype B or unknown serotype)	98.8

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 2003 Reports of Notifiable Diseases. MMWR 2004;53(30):687

11/10/04

Vaccine Coverage Levels – United States, 1962-2004

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

*Previously reported as measles-containing vaccine (MCV).

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. No national coverage data were collected in 1986-1990.

Most recent publication: CDC. National, State, and Urban Area Vaccination Coverage Levels Among Children Aged 19-35 Months – United States, 2004. *MMWR* 2004;54(29);717-721.

APPENDIX H
Standards

Appendix H

Standards for Child and Adolescent Immunization Practices

Copies may be requested from:

Centers for Disease Control and Prevention
National Immunization Program
Resource Center
1600 Clifton Road
Mailstop E-34
Atlanta, GA 30333-0418

Online ordering is available through:
www.cdc.gov/nip/publications

Appendix H

Introduction

In 1992, the National Vaccine Advisory Committee (NVAC), in collaboration with the Ad Hoc Working Group for the Development of Standards for Pediatric Immunization Practices, a working group representing public and private agencies with input from state and local health departments, physician and nursing organizations, and public and private providers, developed a set of standards as to what constitutes the most essential and desirable immunization policies and practices. These standards were endorsed by a variety of medical and public health organizations and represented an important element in our national strategy to protect America's children against vaccine-preventable diseases.

Since that time, vaccine delivery in the US has changed in several important ways. First, vaccination coverage rates among preschool children have increased substantially and are now monitored by the National Immunization Survey.[1,2] Second, vaccination of children has shifted markedly from the public to the private sector,[3,4,5] with an emphasis on vaccination in the context of primary care and the Medical Home.[6]

The Vaccines for Children Program has provided critical support to this shift by covering the cost of vaccinations for the most economically disadvantaged children and adolescents. Third, the development and introduction of performance measures, such as the National Committee for Quality Assurance's HEDIS (Health Plan Employer Data and Information Set),[7] have focused national attention upon the quality of preventive care, including vaccination. Finally, high quality research in health services has helped to refine strategies for raising and sustaining vaccination coverage levels among children, adolescents, and adults.[8]

Health care professionals who vaccinate children and adolescents continue to face important challenges. These challenges include a diminishing level of experience-among patients, parents and physicians-with the diseases that vaccines prevent, the ready availability of vaccine-related information that may be inaccurate or misleading, the increasing complexity of the vaccination schedule, and the failure of many health plans to pay for the costs associated with vaccination. In addition, recommendations from the Advisory Committee on Immunization Practices (ACIP),the American Academy of Pediatrics (AAP), the American Academy of Family Physicians (AAFP) and the American Medical Association (AMA) in 1996 underscore the need to focus on adolescent vaccination.[9]

In this context, NVAC, along with partners representing federal agencies, state and local health departments, and professional organizations, revised and updated the Standards during 2001-02 to reflect these changes and challenges in vaccine delivery. The revision was approved by NVAC on February 8, 2002 and distributed widely among a variety of medical and public health organizations for review and endorsement. More than 40 organizations have formally endorsed the Standards for Child and Adolescent Immunization Practices.

The Standards are directed toward "health care professionals," an inclusive term for the many persons in clinical settings who share in the responsibility for vaccination of children and adolescents: physicians, nurses, mid-level practitioners (e.g., nurse practitioners, physician assistants), medical assistants, and clerical staff. In addition to this primary audience, the Standards are intended to be useful to public health professionals, policy makers, health plan administrators, employers who purchase health care coverage, and others whose efforts shape and support the delivery of vaccination services.

Of note, the use of the term "standards" should not be confused with a minimum standard of care. Rather, these Standards represent the most desirable immunization practices, which health care professionals should strive to achieve. Given current resource limitations, some health care professionals may find it difficult to implement all of the Standards, because of circumstances over which they have little control. The expectation is that, by summarizing best immunization practices in a clear and concise format, the Standards will assist these providers in securing the resources necessary to implement this set of recommendations.

By adopting these Standards, health care professionals can enhance their own policies and practices, making achievement of vaccination objectives for children and adolescents as outlined in Healthy People 2010, a nationwide health promotion and disease prevention agenda from the U.S. Department of Health and Human Services,[10] both feasible and likely. Achieving these objectives will improve the health and welfare of all children and adolescents as well as the communities in which they live.

Standards for Child and Adolescent Immunization Practices

Availability of vaccines

1. Vaccination services are readily available.
2. Vaccinations are coordinated with other health care services and provided in a Medical Home[6] when possible.
3. Barriers to vaccination are identified and minimized.
4. Patient costs are minimized.

Assessment of vaccination status

5. Health care professionals review the vaccination and health status of patients at every encounter to determine which vaccines are indicated.
6. Health care professionals assess for and follow only medically accepted contraindications.

Effective communication about vaccine benefits and risks

7. Parents/guardians and patients are educated about the benefits and risks of vaccination in a culturally appropriate manner and in easy-to-understand language.

Proper storage and administration of vaccines and documentation of vaccinations

8. Health care professionals follow appropriate procedures for vaccine storage and handling.
9. Up-to-date, written vaccination protocols are accessible at all locations where vaccines are administered.
10. Persons who administer vaccines and staff who manage or support vaccine administration are knowledgeable and receive on-going education.
11. Health care professionals simultaneously administer as many indicated vaccine doses as possible.
12. Vaccination records for patients are accurate, complete, and easily accessible.
13. Health care professionals report adverse events following vaccination promptly and accurately to the Vaccine Adverse Event Reporting System (VAERS) and are aware of a separate program, the National Vaccine Injury Compensation Program (VICP).
14. All personnel who have contact with patients are appropriately vaccinated.

Implementation of strategies to improve vaccination coverage

15. Systems are used to remind parents/guardians, patients, and health care professionals when vaccinations are due and to recall those who are overdue.
16. Office- or clinic-based patient record reviews and vaccination coverage assessments are performed annually.
17. Health care professionals practice community-based approaches.

The Standards

Availability of vaccines

1. Vaccination services are readily available.

All health care professionals who provide primary care to children and adolescents should always include routinely recommended vaccines as a part of the care they deliver in the Medical Home.[6]

For some children and adolescents, the main contact with the health care system is not in a primary care provider's office, and therefore, opportunities for vaccination may be missed. Thus, specialists and health care professionals in settings such as schools and school health clinics, sports physical clinics, family planning clinics, sexually transmitted disease (STD) clinics, and substance abuse treatment centers, should assess each patient's vaccination status and either offer indicated vaccines or refer for vaccination if necessary.

Information on vaccines administered outside the primary care setting should be communicated to the primary care provider.

2. Vaccinations are coordinated with other health care services and provided in a Medical Home[6] when possible.

Ideally, vaccines should be given as part of comprehensive health care. In primary care settings, vaccination services should be coordinated with routine well-care visits and other visits. Patients vaccinated in other settings should be encouraged to receive subsequent vaccines in their primary care setting. Patients without a primary care provider should be assisted with identifying one.

3. Barriers to vaccination are identified and minimized.

Barriers to receiving vaccines include delays in scheduling appointments, requiring a well-care visit, long waiting periods in the office, and lack of culturally and age-appropriate educational materials. A physical exam, while an important part of well care, should not be required before administering vaccines: simply observing the patient and questioning about the patient's health status, immunization history, and vaccine contraindications are sufficient. In addition, vaccination-only visits should be available.

Health care professionals should seek advice from parents/guardians and patients to identify ways to make vaccination services easier to use.

4. Patient costs are minimized.

Out-of-pocket costs-including vaccine, administration, and office visit fees-should be as low as possible for all patients, and no child or adolescent should be denied vaccination because of inability to pay.

Resources should be identified to keep patient vaccination costs as low as possible. Free vaccine is available through some public programs, although health care professionals offering these vaccines may charge a reasonable administration fee. Sources of publicly funded vaccines include the Vaccines for Children (VFC) Program, Public Health Service Section 317 grants to States, and state or local programs. Children and adolescents should be screened for their eligibility to receive vaccines through these programs. Vaccinations provided through VFC or Section 317 grants may not be denied because of an inability to pay the administration fee, and health care professionals should assure that parents/guardians and patients are aware of this requirement (applies to all vaccines purchased using Centers for Disease Control and Prevention contracts, regardless of the setting-private or public-in which the vaccines are administered).

To minimize costs for patients, health plans and insurance plans should include the provision and administration of all routinely recommended vaccines as a covered benefit for all children and adolescents. Furthermore, to minimize costs for health care professionals, purchasers and health plans should reimburse health care professionals adequately for delivering vaccines, including the time required for vaccine administration and for communication about vaccine benefits and risks.

** Further information*
CDC maintains a web page about VFC on the Internet at: www.cdc.gov/nip/vfc

Assessment of vaccination status

5. Health care professionals review the vaccination and health status of patients at every encounter to determine which vaccines are indicated.

Health care professionals should review the vaccination status of all patients at all health care visits to minimize the number of missed opportunities to vaccinate. This review should determine if the patient has received any vaccinations elsewhere or is at high risk for disease or undervaccination. This information should be documented in the patient's chart and preventive health summary. Health care professionals who do not offer vaccinations should refer patients to a primary care provider for needed vaccinations.

6. Health care professionals assess for and follow only medically accepted contraindications.

Withholding vaccinations due to medical concerns that are not contraindications results in missed opportunities for prevention. Health care professionals should ask about any condition or circumstance that might indicate a vaccination should be withheld or delayed and about prior adverse events temporally associated with any vaccination.

Health care professionals should support their decisions about what constitutes a contraindication or deferral for each vaccine by consulting the Guide to Contraindications to Vaccinations published by CDC (available on the Internet at: www.cdc.gov/nip/recs/contraindications.pdf), the harmonized recommendations of the ACIP, AAP,and AAFP (available on the Internet at: www.cdc.gov/nip/recs/child-schedule.htm#Printable), the AAP's Red Book, and other relevant recommendations, Vaccine Information Statements, and manufacturers' package inserts. Contraindications and deferrals should be documented in the medical record.

Effective communication about vaccine benefits and risks

7. Parents/guardians and patients are educated about the benefits and risks of vaccination in a culturally appropriate manner and in easy-to-understand language.

Health care professionals should allow sufficient time with parents/guardians and adolescent patients to discuss the benefits of vaccines, the diseases they prevent, any known risks from vaccines, the immunization schedule and the need to receive vaccines at the recommended ages, and the importance of bringing the patient's hand-held vaccination record to each health care visit. Health care professionals should encourage parents/guardians and adolescent patients to take responsibility for ensuring that the patient is fully vaccinated.

For all commonly used childhood vaccines, all health care professionals are required by federal law to give Vaccine Information Statements (VIS) to vaccine recipients or their parents/guardians at each visit. A VIS is a vaccine-specific, two-page information sheet, produced by CDC, which describes the benefits and risks of a vaccine. If necessary, health care professionals should supplement the VIS with oral explanations or other written materials that are culturally and linguistically appropriate. Health care professionals should review written materials with patients and their parents/guardians and address questions and concerns.

Health care professionals should encourage parents/guardians and adolescent patients to inform the health care professional of adverse events following the vaccine to be administered and explain how to obtain medical care, if necessary.
See Standard 13 for a description of the Vaccine Adverse Events Reporting System (VAERS).

* *Further information*
General vaccination information for health care professionals, parents, and members of the public may

be obtained by calling the CDC National Immunization Information Hotline at 1-800-232-2522 (English) or 1-800-232-0233 (Spanish). Information about vaccine risk communication for health care professionals can be found on the Internet at: www.cdc.gov/nip/vacsafe/research/peds.htm and in the latest edition of the Red Book. Vaccine Information Statements are available in English and numerous other languages from State health departments and on the Internet at: www.cdc.gov/nip/publications/VIS/default.htm and www.immunize.org
Recommendations for national standards for culturally and linguistically appropriate services (CLAS) in health care may be found on the Internet at: www.omhrc.gov/omh/programs/2pgprograms/finalreport.pdf

Proper storage and administration of vaccines and documentation of vaccinations

8. Health care professionals follow appropriate procedures for vaccine storage and handling.

Vaccines should be handled and stored as recommended in the manufacturers' package inserts; the expiration date for each vaccine should be noted. Temperatures at which vaccines are stored and transported should be monitored and recorded twice daily. Summary information about vaccine storage and handling procedures are also available from state and local health departments and CDC.

Health care professionals should monitor vaccine inventory and undertake efforts to reduce wastage and loss.

* *Further information*
CDC-recommended storage and handling procedures are available from CDC by calling 404-639-8222.

9. Up-to-date, written vaccination protocols are accessible at all locations where vaccines are administered.

To promote the safe and effective use of vaccines, health care professionals should maintain written protocols that detail the following: vaccine storage and handling; the recommended vaccination schedule, vaccine contraindications, and administration techniques; treatment and reporting of adverse events; vaccine benefit and risk communication; and vaccination record maintenance and accessibility.
These protocols should be consistent with established guidelines, reviewed frequently, and revised as needed to assure that they remain up-to-date.

10. Persons who administer vaccines and staff who manage or support vaccine administration are knowledgeable and receive on-going education.

Health care professionals or others who administer vaccinations should be knowledgeable and receive continuing education in vaccine storage and handling; the recommended vaccine schedule, contraindications, and administration techniques; treatment and reporting of adverse events; vaccine benefit and risk communication; and vaccination record maintenance and accessibility. With appropriate training, and in accordance with state law/regulation/policy, persons other than physicians and nurses may administer vaccines. In addition, other staff should receive training and continuing education related to their specific roles and responsibilities that affect vaccination services.

* *Further information CDC sponsors distance-based training opportunities (e.g., satellite broadcasts, web-based training, videotapes, self-administered print materials) for health care professionals. Information about training is available on the Internet at: www.cdc.gov/nip/ed*

11. Health care professionals simultaneously administer as many indicated vaccine doses as possible.

Administering vaccines simultaneously (at the same visit), in accordance with recommendations from the Advisory Committee on Immunization Practices, the American Academy of Pediatrics, and the American Academy of Family Physicians, is safe, effective, and indicated. Although the immunization schedule provides age flexibility for administering certain vaccine doses, simultaneous administration decreases the number of visits needed and the potential for missed doses, and enables earlier protection. When indicated vaccines are not simultaneously administered, arrangements should be made for the patient's earliest return to receive the needed vaccination(s).

* *Further information*
Additional information on the safety of simultaneous vaccination may be found on the Internet at: www.cdc.gov/nip/vacsafe/research/simultaneous.htm

12. Vaccination records for patients are accurate, complete, and easily accessible.

Vaccination records for patients should be recorded on a standard form in an easily accessible location in the medical record to facilitate rapid review of vaccination status. Accurate record keeping helps to ensure that only needed vaccinations are given. As required by federal law (42 US Code 300aa-25), health care professionals should assure that records contain the following information for each vaccination: the date of administration, the vaccine manufacturer and lot number, the signature and title of the person administering the vaccine, and the address where the vaccine was given. Vaccine refusal should also be documented.

The medical record maintained by the primary care provider should document all vaccines received, including those received at a specialist's office or in another health care setting. When a health care professional who does not routinely care for a patient vaccinates that patient, the patient's primary care provider should be informed.

All vaccinations administered should be reported to state or local immunization registries, where available, to ensure that each patient's vaccination history remains accurate and complete. Registries also may be useful for verifying the vaccination status of new patients, determining which vaccines are needed at a visit, printing official records, and providing reminders and recalls to parents.

Health care professionals should assure that each patient has a hand-held vaccination record that documents each vaccine received, including the date and the name of the health care professional who administered the vaccine. Health care professionals should encourage parents/guardians and adolescent patients to bring the patient's hand-held record to each health care visit so it can be updated.

* *Further information*
The CDC maintains an Immunization Registry Clearinghouse. Information about this clearinghouse is available on the Internet at: www.cdc.gov/nip/registry/

13. Health care professionals report adverse events following vaccination promptly and accurately to the Vaccine Adverse Event Reporting System (VAERS) and are aware of a separate program, the National Vaccine Injury Compensation Program (VICP).

Health care professionals should promptly report all clinically significant adverse events following vaccination to the Vaccine Adverse Event Reporting System (VAERS) even if the health care professional is not certain that the vaccine caused the event. Health care professionals should document in detail the adverse event in the patient's medical record as soon as possible. Providers should be aware that parents/guardians and patients may report to VAERS, and that if they choose to do so, they are encouraged to seek the help of their health care provider.

The National Vaccine Injury Compensation Program (VICP) is a no-fault system that compensates persons of any age for injuries or conditions that may have been caused

by a vaccine recommended by CDC for routine use in children. Health care professionals should be aware of the VICP in order to address questions raised by parents/guardians and patients.

Since VAERS and VICP are separate programs, a report of an event to VAERS does not result in the submission of a compensation claim to VICP. A brief description and contact information for both programs is provided on each Vaccine Information Statement for those vaccines covered by the National Childhood Vaccine Injury Act.

* *Further information*
Information about VAERS, as well as guidance about how to obtain and complete a VAERS form can be found on the Internet: www.vaers.org or by calling 1-800-822-7967. Information about the VICP is available on the Internet at: www.hrsa.gov/osp/vicp or by calling 1-800-338-2382.

14. All personnel who have contact with patients are appropriately vaccinated.

Health care professionals and other personnel who have contact with patients should be appropriately vaccinated. Offices and clinics should have policies to review and maintain the vaccination status of staff and trainees.

* *Further information*
ACIP recommendations for vaccinating health care workers are available on the Internet at: ftp://ftp.cdc.gov/pub/publications/mmwr/rr/rr4618.pdf

Implementation of strategies to improve vaccination coverage

15. Systems are used to remind parents/guardians, patients, and health care professionals when vaccinations are due and to recall those who are overdue.

Evidence demonstrates that reminder/recall systems improve vaccination coverage.[11]

Patient reminder/recall interventions inform individuals that they are due (reminder) or overdue (recall) for specific vaccinations. Patient reminders/recalls can be mailed or communicated by telephone; an autodialer system can be used to expedite telephone reminders. Patients who might be at high risk for not complying with medical recommendations, for example those who have missed previous appointments, should receive more intensive follow-up.

Similarly, provider reminder/recall systems alert health care professionals when vaccines are due or overdue. Notices should be placed in patient charts or communicated to health care professionals by computer or other means. Immunization registries can facilitate automatic generation of reminder/recall notices.

16. Office- or clinic-based patient record reviews and vaccination coverage assessments are performed annually.

Evidence shows that assessments are most effective in improving vaccination coverage in a practice when they combine chart reviews to determine coverage with the provision of results to health care professionals and staff.[11]

Effective interventions also may incorporate incentives or compare performance to a goal or standard. Coverage should be assessed regularly so that reasons for low coverage in the practice, or in a sub-group of patients, are identified and addressed. For assistance in conducting vaccination coverage assessments, health care professionals should contact their state or local immunization program.

17. Health care professionals practice community-based approaches.

All health care professionals share in the responsibility to achieve the highest possible degree of community protection against vaccine-preventable diseases.

Immunization protects the entire community as well as the individual. No community is optimally protected against vaccine-preventable diseases without high vaccination coverage. Therefore, health care professionals should consider the needs of the community (especially underserved populations) as well as those of their patients. Community-based approaches may involve working with partners in the community, including public health departments, managed care organizations, other service providers such as the US Department of Agriculture's Special Supplemental Nutrition Program for Women, Infants, and Children (WIC), advocacy groups, schools, and service organizations to determine community needs and develop vaccination services that address these needs.

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Organizations providing endorsement for the revised Standards for Child and Adolescent Immunization Practices

Advisory Committee on Immunization Practices

Albert B. Sabin Vaccine Institute

Ambulatory Pediatric Association

American Academy of Family Physicians

American Academy of Pediatrics

American Academy of Physician Assistants

American College of Emergency Physicians

American College of Osteopathic Pediatricians

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Association of Maternal and Child Health Programs

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The NVAC is composed of 15 members from public and private organizations representing vaccine manufacturers, physicians, parents, and state and local health agencies. In addition, representatives from governmental agencies involved in health care or allied services serve as ex-officio members of the NVAC.

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Georges Peter, MD (Chair)
Brown Medical School
Providence, RI

Ann Margaret Arvin, MD
Stanford University School of Medicine Stanford, CA

Jeffrey P. Davis, MD
Wisconsin Division of Health
Madison, WI

Michael D. Decker, MD, MPH
Aventis Pasteur
Swiftwater, PA

Patricia Fast, MD, PhD
International AIDS Vaccine Initiative
New York, NY

Fernando A. Guerra, MD, MPH
San Antonio Metropolitan Health District
San Antonio, TX

Charles M. Helms, MD, PhD
University of Iowa Hospital and Clinics
Iowa City, IA

Alan Richard Hinman, MD
The Task Force for Child Survival and Development
Decatur, GA

Ruth Katz, JD, MPH
Yale University School of Medicine
New Haven, CT

Jerome O. Klein, MD
Boston Medical Center
Boston MA

Mary Beth Koslap-Petraco, MS, CPNP Suffolk County Department of Health Services
Lindenhurst, NY

Peter R. Paradiso, PhD
Wyeth-Lederle Vaccines and Pediatric American Home Products
West Henrietta, NY

William Schaffner, MD
Vanderbilt University School of Medicine
Nashville, TN

Patricia N. Whitley-Williams, MD
Robert Wood Johnson Medical School New Brunswick, NJ

Donald E. Williamson, MD
Alabama Department of Public Health Montgomery, AL

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Steven Black, MD
Kaiser Permanente Study Center
Oakland, CA
(representing the American Association of Health Plans)

Jackie Noyes
American Academy of Pediatrics
Washington, DC
(representing the Advisory Commission on Childhood Vaccines)

David S. Stevens, MD
Emory University School of Medicine Atlanta, GA
(representing the Vaccines and Related Biological Products Advisory Committee)

Robert Daum, MD
University of Chicago Children's Hospital
Chicago, IL
(representing the Vaccines and Related Biological Products Advisory Committee)a

John F. Modlin, MD
Dartmouth Medical School
Lebanon, NH
(representing the Advisory Committee on Immunization Practices)

Karen Midthun, MD
Food and Drug Administration
Rockville, MD

Col Renata J.M. Engler
Walter Reed Medical Center
Washington, DC

Carole Heilman, PhD
National Institute of Allergy and
Infectious Diseases
Bethesda, MD

Geoffrey Evans, MD
Health Resources and Services Administration
Rockville, MD

Ruth Frischer, PhD
US Agency for International Development
Washington, DC

T. Randolph Graydon
Centers for Medicare and Medicaid Services
Baltimore, MD

Walter A. Orenstein, MD
Centers for Disease Control and Prevention
Atlanta, GA

William A. Robinson, MD
Health Resources and Services Administration
Rockville, MD

Emily Marcus Levine
Office of the General Counsel
Department of Health and Human Services
Rockville, MD

aFormer liaison representative to NVAC

Standards for Adult Immunization Practices

Copies may be requested from:

Centers for Disease Control and Prevention
National Immunization Program
Resource Center
1600 Clifton Road
Mailstop E-34
Atlanta, GA 30333-0418

Online ordering is available through:
www.cdc.gov/nip/publications

The Standards for Adult Immunization Practices
are also published in
the *American Journal of Preventive Medicine* 2003;25(2)

Appendix H

Introduction

As a result of successful immunization practices geared toward infants and children in the United States, the incidence of childhood vaccine-preventable diseases has declined dramatically. However, similar success among adults has not been achieved.

All adults should be immune to measles, mumps, rubella, tetanus, diphtheria, and varicella. All those aged 50 or older, and younger persons at high risk should receive influenza vaccine annually; all those aged 65 or older, and younger persons at high risk, should receive pneumococcal vaccine. Adults susceptible to hepatitis A, hepatitis B, and polio should be vaccinated if they are at risk for exposure to an infection. Ideally, recommended vaccines should be given to all adults as a routine part of health care.

Adults suffer the vast majority of vaccine-preventable disease in the U.S. During average influenza seasons, up to 40 million Americans may suffer from influenza infection, approximately 100,000 are hospitalized, and approximately 40,000 die of influenza and its complications.[1,2] Pneumococcal infections account for 100,000 to 135,000 hospitalizations for pneumonia, more than 60,000 cases of bacteremia and other forms of invasive disease, and about 7,000 death from invasive pneumococcal disease each year.[3,4,5] More than 75,000 persons, mostly adolescents and adults, contract hepatitis B each year.[6,7] There are approximately 4,000 to 5,000 deaths due to hepatitis B each year, mainly among adults.[8] Approximately 8 million young women are unprotected against rubella, putting their infants at risk for congenital rubella syndrome if these women should become pregnant.[9] Up to half of all Americans age 50 and older have not received all of their recommended immunizations against tetanus and diphtheria.[10]

Today, vaccines are safe, effective, and readily available. Benefits of vaccination include reduced disease incidence, morbidity and mortality, and reduced health care costs. However, vaccines remain underutilized among adults, especially among persons at high risk for infection and complications of disease, and among certain racial/ethnic populations. For instance, the rates of influenza and pneumococcal vaccination in African American and Hispanic populations are significantly lower than those among whites.[11]

The U.S. Department of Health and Human Services' Healthy People 2010 outlines a comprehensive, nationwide health promotion and disease prevention agenda.[12] There are 8 objectives that relate to adult immunizations or vaccine-preventable diseases. Achieving these objectives will require a dramatic increase from current coverage levels.

For example, for influenza and pneumococcal vaccination of adults age 65 and older, the target coverage is 90% for annual influenza immunization and 90% for one dose of pneumococcal vaccine. In 2002, national statistics demonstrated rates of only 66% and 56%, respectively.13 Among adults aged 65 years or less at high risk due to medical, behavioral, or environmental risk factors, even greater increases will be required to reach the 2010 targets.

Appendix H

In 1990, the National Coalition for Adults Immunization (NCAI) developed the first Standards for Adult Immunization Practices, which were endorsed by more than 60 professional organizations from the public and private sectors.[14] In January 1994, the National Vaccine Advisory Committee (NVAC) reviewed the status of adult immunization in the United States and presented specific goals and recommendations for improvement.[15] In 2000, NVAC issued a report on adult immunization programs in nontraditional settings. This report included quality standards for these programs as well as guidance for program evaluation.[16]

To reflect the recommendations and standards in these recent reports and the Healthy People 2010 coverage goals, the NVAC and NCAI have revised the 1990 Standards. The revised Standards are more comprehensive than the previous version and evidence-based medicine has been used to support these Standards wherever possible.[17] The Standards supplement research with expert consensus in areas where research does not offer guidance but experience does.

Today, more tools are available to support immunization providers. The revised Standards include links to web sites that contain information on model standing order policies, instructions for setting up reminder/recall systems, and templates for personal vaccination records.

The revised Standards for Adult Immunization Practices provide a concise, convenient summary of the most desirable immunization practices. The Standards have been widely endorsed by major professional organizations. This revised version of the Standards for Adult Immunization Practices is recommended for use by all health care professionals and payers in the public and private sectors who provide immunizations for adults. Everyone involved in adult immunization should strive to follow these Standards. Not all practices and programs have the resources necessary to fully implement the Standards, nevertheless, those lacking the resources should find the Standards useful to guide current practice and to guide the process of defining immunization needs and obtaining additional resources in the future.

Standards for Adult Immunization Practices

Make vaccinations available

1. Adult vaccination services are readily available.
2. Barriers to receiving vaccines are identified and minimized.
3. Patient "out of pocket" vaccination costs are minimized.

Assess patients' vaccination status

4. Health care professionals routinely review the vaccination status of patients.
5. Health care professionals assess for valid contraindications.

Communicate effectively with patients

6. Patients are educated about risks and benefits of vaccination in easy-to-understand language.

Administer and document vaccinations properly

7. Written vaccination protocols are available at all locations where vaccines are administered.
8. Persons who administer vaccines are properly trained.
9. Health care professionals recommend simultaneous administration of all indicated vaccine doses.
10. Vaccination records for patients are accurate and easily accessible.
11. All personnel who have contact with patients are appropriately vaccinated.

Implement strategies to improve vaccination rates

12. Systems are developed and used to remind patients and health care professionals when vaccinations are due and to recall patients who are overdue.
13. Standing orders for vaccinations are employed.
14. Regular assessments of vaccination coverage levels are conducted in a provider's practice.

Partner with the community

15. Patient-oriented and community-based approaches are used to reach target populations.

The Standards

Make Vaccinations Available

Standard 1: *Adult vaccination services are readily available*
Primary care health care professionals who serve adults should always include routinely recommended vaccinations as part of their care. Specialists, whose patients may be at increased risk of vaccine-preventable diseases, also should include routinely recommended vaccinations as part of their care. For selected vaccines (e.g., meningococcal vaccine for college entrants, vaccines for international travelers) patients may be referred to another provider.

Standard 2: *Barriers to receiving vaccines are identified and minimized*
Barriers to receiving vaccines may include requiring a physical examination before vaccination, requiring an additional visit for vaccination, long waiting periods, and lack of educational materials that are culturally appropriate. Prior to vaccine administration, simply observing the patient, asking if the patient is well and questioning the patient/guardian about vaccine contraindications is sufficient.

Standard 3: *Patient "out of pocket" vaccination costs are minimized*
Resources should be identified to keep patient vaccination costs as low as possible, specifically for those patients aged 65 years or older and for vaccines not covered by Medicare Part B.

In the public sector, patient fees should include only the cost of vaccine and administration that cannot be funded through another source. In the private sector, routinely recommended vaccination services should be included in basic benefits packages. System and policy changes should be addressed to provide adequate reimbursement to providers for delivering vaccinations to their adult population.

Assess Patients' Vaccination Status

Standard 4: *Health care professionals routinely review the vaccination status of patients*
Health care professionals should review and document the vaccination status of all new patients during initial office visits and also review vaccination status on an annual basis thereafter. Health care professionals should ascertain if the patient has medical risk factors, lifestyle risk factors, or an occupation for which certain vaccines may be indicated. Health care professionals should record this information in the patient's chart and preventive health summary. Health care professionals should routinely review pneumococcal vaccination status at the time of influenza vaccination.

Standard 5: *Health care professionals assess for valid contraindications*
Failure to differentiate between valid and invalid contraindications often results in the needless deferral of indicated vaccinations. Health care professionals should ask about prior adverse

events in connection with a vaccination and about any conditions or circumstances that might indicate vaccination should be withheld or delayed. Health care professionals should refer to current Advisory Committee on Immunization Practices (ACIP) recommendations on valid and invalid contraindications as well as on valid indications for vaccine use (www.cdc.gov/nip).

Communicate Effectively with Patients

Standard 6: *Patients are educated about risks and benefits of vaccination in easy-to-understand language*

Health care professionals should discuss with the patient the benefits of vaccines, the diseases that they prevent, and any known risks from vaccines. These issues should be discussed in the patient's native language, whenever possible. Printed materials, accurately translated into the patient's language should be provided. For most commonly used vaccines, the U.S. Federal Government has developed Vaccine Information Statements for use by both public and private health care professionals to give to potential vaccine recipients. For vaccines covered by the National Childhood Vaccine Injury Act, including those vaccines used in children, these forms are required. These statements are available in English and other languages. Health care professionals should allot ample time with patients to review written materials and address questions and concerns. Information and assistance can be obtained by calling the Immunization Hotline (1-800-232-2522) or accessing the website (www.cdc.gov/nip).

Health care professionals should respect each patient's right to make an informed decision to accept or reject a vaccine or defer vaccination until more information is collected.

Administer and Document Vaccinations Properly

Standard 7: *Written vaccination protocols are available at all locations where vaccines are administered*

The medical protocol should detail procedures for vaccine storage and handling, vaccine schedules, contraindications, administration techniques, management and reporting of adverse events, and record maintenance and accessibility. These protocols should be consistent with established guidelines. CDC-recommended storage and handling procedures are available on the Internet at: www.gravity.lmi.org/lmi_cdc/geninfo.htm.

Health care professionals should promptly report all clinically significant adverse events following vaccination to the Vaccine Adverse Event Reporting System (VAERS), even if the health care professional does not believe that the vaccine caused the event.

Reporting is required for those vaccines given to adults and medical conditions covered by the National Childhood Vaccine Injury Act of 1986, as amended. Health care professionals should be aware that patients may report to VAERS, and that if they choose to do so, they are encouraged to seek the help of their health care professional. Report forms and assistance are available by calling 1-800-822-7967 or on the Internet at www.fda.gov/cber/vaers/vaers.htm.

The National Vaccine Injury compensation Program (VICP) is a no-fault system that compensates persons of any age for injuries or conditions that may have been caused by a vaccine recommended by CDC for routine administration to children. Health care professionals should be aware of the VICP in order to address questions raised by patients. Information about the VICP is available on the internet at www.hrsa.gov/osp/vicp.htm or by calling 1-800-338-2382.

Since VAERS and VICP are separate programs, a report of an event to VAERS does not result in the submission of a compensation claim to VICP. Such a claim must be filed independently in the U.S. Court of Federal Claims. A brief description and contact information for both programs is provided on each Vaccine Information Statement for
vaccines covered by the VICP.

Standard 8: *Persons who administer vaccines are properly trained*
All persons who administer vaccinations should be fully trained in vaccine storage and handling, vaccine schedules, contraindications, administration techniques, management and reporting of adverse events, and record maintenance and accessibility. Office staff should receive continuing education on these issues annually. With appropriate training, persons other than physicians and nurses can administer vaccines. Health care professionals should contact public health authorities or other medical authorities in their state for more information concerning which individuals are permitted to administer vaccines.

Standard 9: *Health care professionals recommend simultaneous administration of all indicated vaccine doses*
Administering indicated vaccines simultaneously is safe and effective. Simultaneous administration decreases the number of required visits and the potential for missed doses. Measles, mumps, and rubella (MMR) vaccine and tetanus and diphtheria (Td) toxoids should always be administered in their combined product. Giving influenza and pneumococcal vaccine at the same time (but in separate arms) is also safe and effective. Health care professionals should respect the choices of patients and their caregivers.

Standard 10: *Vaccination records for patients are accurate and easily accessible*
Patient vaccination histories should be recorded on a standard form in an easily accessible location in the medical record to facilitate rapid review of vaccination status. Accurate record keeping helps ensure that needed vaccinations are administered and unnecessary vaccinations are not administered. Records should indicate the vaccine, the date of administration, the vaccine manufacturer and lot number, the signature and title of the person administering the vaccine, and the address where the vaccine was administered. The medical record at the primary care provider's office, clinic or worksite should include all vaccinations received (such as those received at a specialist's office, influenza vaccination clinic, or pharmacy).
Record keeping may be paper-based or computerized. Computer systems make record maintenance, retrieval, and review easier.

Health care professionals should give patients a personal record of vaccinations they have received, including the dates and places of administration. Patients should be encouraged to bring their vaccination records to all medical visits.

Information and a modifiable template of these forms and records are available at www.ahcpr.gov/ppip/adultflow.pdf and are also available on CD-ROM and can be ordered on the internet: www.atpm.org/Immunization/whatworks.html

Standard 11: *All personnel who have contact with patients are appropriately immunized*
Health care professionals and other personnel (including first responders) who have contact with patients should be appropriately immunized (e.g., annual influenza vaccination, hepatitis B vaccination). Institutions should have policies to review and maintain the appropriate vaccination of staff and trainees.

ACIP recommendations for vaccinating health care workers are available on the Internet: www.cdc.gov/nip/publications/ACIP-list.htm

Implement Strategies to Improve Vaccination Rates

Standard 12: *Systems are developed and used to remind patients and health care professionals when vaccinations are due and to recall patients who are overdue*
Evidence shows that reminder/ recall systems improve adult vaccination rates. Systems may be designed to alert patients who are due (reminder) or overdue (recall) for specific vaccine doses or they may alert patients to contact their provider to determine if vaccinations are needed. Reminders or recalls can be mailed or communicated by telephone; an autodialer can be used to expedite telephone reminders. Patients who might be at high risk for not complying with medical recommendations may require more intensive follow-up.

Provider reminder/recall interventions inform those who administer vaccinations that individual patients are due or overdue for specific vaccinations. Reminders can be delivered in patient charts, by computer, and/or by mail or other means, and content of the reminders can be specific or general.

Information about these strategies and resources to assist in their implementation are available on CD-ROM and can be ordered on the internet: www.atpm.org/Immunization/whatworks.html. Model reminder recall templates are also available at www.ahcpr.gov/ppip/postcard.pdf

Standard 13: *Standing orders for vaccinations are employed*
Evidence shows that standing orders improve vaccination coverage among adults in a variety of health care settings, including nursing homes, hospitals, clinics, doctor's offices, and other institutional settings. Standing orders enable non-physician personnel such as nurses and pharmacists to prescribe or deliver vaccinations by approved protocol without direct physician involvement at the time of the interaction. Standing orders overcome administrative barriers such as lack of physician personnel to order vaccines. Further, the Centers for Medicare and Medicaid allow standing order exemption from medicare rules www.cms.hhs.gov/medicaid/ltcsp/sc0302.pdf)

Information about this strategy and its implementation is available on CD-ROM and can be ordered on the internet: www.atpm.org/Immunization/whatworks.html

Standard 14: *Regular assessments of vaccination coverage rates are conducted in a provider's practice*
Evidence shows that assessment of vaccination coverage and provision of the results to the staff in a practice improves vaccination coverage among adults. Optimally, such assessments are performed annually. Provider assessment can be performed by the staff in the practice or by other organizations including state and local health departments. Effective interventions that include assessment and provision of results also may incorporate incentives or comparing performance to a goal or standard. This process is commonly referred to as AFIX (Assessment, Feedback, Incentives, and Exchange of Information). Coverage should be assessed regularly so that reasons for low coverage in the practice, or in a sub-group of the patients served, can be identified and interventions implemented to address them.

Information about this strategy and its implementation is available on CD-ROM and can be ordered on the internet: www.atpm.org/Immunization/whatworks.html

Software to assist in conducting coverage rate assessments and feedback is available at: www.cdc.gov/nip

Partner with the Community

Standard 15: *Patient-oriented and community-based approaches are used to reach target populations*
Vaccination services should be designed to meet the needs of the population served. For example, interventions that include community education, along with other components, such as extended hours, have been demonstrated to improve vaccination coverage among adults. Vaccination providers can work with partners in the community, including other health professionals (e.g., pharmacists), vaccination advocacy groups, managed care organizations, service organizations, manufacturers, and state and local health departments to determine community needs and develop vaccination services to address them.

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Endorsements

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Brown Medical School
Providence, RI

Ann Margaret Arvin, MD
Stanford University School of Medicine Stanford, CA

Jeffrey P. Davis, MD
Wisconsin Division of Health
Madison, WI

Michael D. Decker, MD, MPH
Aventis Pasteur
Swiftwater, PA

Patricia Fast, MD, PhD
International AIDS Vaccine Initiative
New York, NY

Fernando A. Guerra, MD, MPH
San Antonio Metropolitan Health District
San Antonio, TX

Charles M. Helms, MD, PhD
University of Iowa Hospital and Clinics
Iowa City, IA

Alan Richard Hinman, MD
The Task Force for Child Survival and Development
Decatur, GA

Ruth Katz, JD, MPH
Yale University School of Medicine
New Haven, CT

Jerome O. Klein, MD
Boston Medical Center
Boston MA

Mary Beth Koslap-Petraco, MS, CPNP
Suffolk County Department of
Health Services
Lindenhurst, NY

Peter R. Paradiso, PhD
Wyeth-Lederle Vaccines and Pediatric American Home Products
West Henrietta, NY

William Schaffner, MD
Vanderbilt University School of Medicine
Nashville, TN

Patricia N. Whitley-Williams, MD
Robert Wood Johnson Medical School New Brunswick, NJ

Donald E. Williamson, MD
Alabama Department of Public Health Montgomery, AL

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Kaiser Permanente Study Center
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Robert Daum, MD
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Geoffrey Evans, MD
Health Resources and Services Administration
Rockville, MD

Ruth Frischer, PhD
US Agency for International Development
Washington, DC

T. Randolph Graydon
Centers for Medicare and Medicaid Services
Baltimore, MD

Walter A. Orenstein, MD
Centers for Disease Control
and Prevention
Atlanta, GA

William A. Robinson, MD
Health Resources and Services Administration Rockville, MD

Emily Marcus Levine
Office of the General Counsel
Department of Health and
Human Services
Rockville, MD

aFormer liaison representative to NVAC

Executive and Writing Committee

Gregory A. Poland, MD
Mayo Clinic and Foundation
Rochester, MN.

Abigail M. Shefer, MD
National Immunization Program
Centers for Disease Control and Prevention
Atlanta, GA

Peggy S. Webster, MD
Abbott Laboratories, Abbott Park, IL
(formerly of the National Coalition for Adult Immunization).

Mary McCauley, MTSC
National Immunization Program
Centers for Disease Control and Prevention
Atlanta, GA

Edward W. Brink, MD
National Immunization Program
Centers for Disease Control and Prevention
Atlanta, GA

Marc LaForce, MD
Bill and Melinda Gates Foundation
Seattle, WA (formerly of BASICS II, Arlington, VA)

Dennis J. O'Mara
National Immunization Program
Centers for Disease Control and Prevention
Atlanta, GA

James A. Singleton, MS
National Immunization Program
Centers for Disease Control and Prevention
Atlanta, GA

Raymond A. Strikas, MD
National Immunization Program
Centers for Disease Control and Prevention
Atlanta, GA

Patricia N. Whitley-Williams, MD
University of Medicine and Dentistry of New Jersey - Robert Wood Johnson
Medical School,
New Brunswick, NJ

Georges Peter, MD
Brown Medical School
Providence, RI

Essential Public Health Services

"The individuals who work in public health have entered the field from many professional disciplines—medicine, nursing, law, dentistry, teaching, social work, and even the ministry. When there's a straightforward task to be done—inspecting restaurants, handing out a WIC voucher, or checking vital signs—it's easy for everyone to see the purpose of public health and understand it. It's much harder for staff to understand the "why" of public health—why we give immunizations, why community assessments are important, and how all the work of public health is interconnected."
- Local health deparement director

The U.S. public health workforce consists of approximately 500,000 individuals currently employed by a range of organizations involved in public health practice, including governmental public health agencies, other public sector agencies, health care delivery organizations, voluntary organizations, community-based groups, academia, and other entities. The public health workforce is defined less by where they work than by what they do, which is to provide essential public health services to communities throughout the nation. The essential services were listed in a statement, *Public Health in America* in 1994.

The Public Health Functions Steering Committee, comprising representatives of several national organizations and federal agencies involved in public health, developed *Public Health in America* as a consensus statement "to explain what public health is; clarify the essential role of public in the overall health system; and provide accountability by linking public health performance to health outcomes." The statement provides a common vision for public health, **"Healthy People in Healthy Communities"** as well as a mission, **"To promote physical and mental health and prevent disease, injury and disability."** The Essential Public Health Services provides a list of ten public health services that define the practice of public health. (Table 1)

Since 1994, there is momentum around using the Essential Services framework. It has already been proven to be valuable in assessing organizational capacity, job performances and expenditures. There is more work needed to increase the usefulness of this framework. One promising area is the use of the essential services to identify the general knowledge, skills and abilities (i.e., core competencies) that are needed by public health workers regardless of where they work or their specific role, background or programmatic responsibility. Examples of core competencies include epidemiology, health communications/social marketing, community needs assessment, and mobilization.

As one state health director explained, *"Historically, we've generally done a good job of tasks like screening children or treating STDs and TB. We haven't done as well with some other tasks critical to improving the public's health, because our people lack the skills to convene and talk to community groups, analyze and explain data, sit at a policy table, or assess community needs."* It has been estimated that almost 4 out of 5 public health workers nationwide are under trained in the disciplines of public health. A major challenge in the 21st century will be to ensure that all public health workers have access to the training and continuing education needed to perform the essential services. Your participation in "Epidemiology and Prevention of Vaccine Preventable Diseases" contributes directly to competent delivery of the essential services of public health. As part of the public health team, your role is broad and more complicated than just providing personal health services. You are helping the community create conditions in which everyone can be healthy.

To learn about the **Public Health Functions Project**, visit their website at http://web.health.gov/phfunctions

Table 1. Ten Essential Public Health Services

1. **Monitor health** status to identify community health problems.
2. **Diagnose and investigate** health problems and health hazards in the community.
3. **Inform, educate and empower** people about health issues.
4. **Mobilize community partnerships** to identify and solve health problems.
5. **Develop policies and plans** that support individual and community health efforts.
6. **Enforce laws** and regulations that protect health and ensure safety.
7. **Link** people **to** needed personal health **services and** assure the provision of health **care** when otherwise unavailable.
8. **Assure a competent** public health and personal health workforce.
9. **Evaluate** effectiveness, accessibility, and quality of personal and population-based health services.
10. **Research** for new insights and innovative solutions to health problems.

Public Health Functions Steering Committee, Public Health in America, July 1995

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Special Communication

Adult Immunization

Summary of the National Vaccine Advisory Committee Report

David S. Fedson, MD, for the National Vaccine Advisory Committee

In January 1994 the National Vaccine Advisory Committee adopted a report that reviewed the status of adult immunization in the United States. Vaccine-preventable infections of adults represent a continuing cause of morbidity and mortality. Their major impact is among older persons. Effective and safe vaccines against these diseases are available, but they are poorly used. Several reasons account for low immunization levels among adults, including inadequate awareness by health care providers and the public of the importance and benefits of vaccination. Health care providers often fail to take advantage of opportunities to immunize adults during office, clinic, and hospital contacts and fail to organize programs in medical settings that ensure adults are offered the vaccines they need. Inadequate reimbursement for adult immunization by public and private health insurers and a lack of federal programs to support vaccine delivery are also major problems. The National Vaccine Advisory Committee's report includes five goals and 18 recommendations for improving adult immunization. To reach the Public Health Service adult immunization goals for the year 2000, the Committee recommends (1) improvements in public and provider education; (2) major changes in clinical practice; (3) increased financial support by public and private health insurers; (4) improved surveillance of vaccine-preventable diseases and vaccine production and delivery; and (5) support for research on vaccine-preventable diseases, new and improved vaccines, immunization practices, and international programs for adult immunization.

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IMMUNIZATION programs in the United States have dramatically reduced the occurrence of many childhood infectious diseases (Table 1).[1,2] Diphtheria and childhood tetanus have practically disappeared, and fatal cases of pertussis (whooping cough) are rare.[3] No cases of indigenous poliomyelitis have been reported since 1979.[4] The occurrence of measles has been substantially reduced.[5] Cases of childhood rubella are rarely observed, and there are few reports of congenital rubella syndrome.[6] Childhood mumps is seldom encountered by physicians.[7] The recent extraordinary decline in *Haemophilus influenzae* type b meningitis is largely attributable to widespread use of *Haemophilus influenzae* type b vaccines.[8] Nonetheless, the reemergence of measles during the period 1989 through 1991,[5] the persistence of congenital rubella syndrome,[6] and lingering questions about the safety of pertussis vaccine[9] are sobering reminders that control of vaccine-preventable childhood diseases requires constant vigilance. Our nation has responded with an unhesitating commitment of resources to expand our immunization efforts, most notably the president's Childhood Immunization Initiative.[10]

The contrast between the impact of vaccine-preventable diseases of adults compared with those of children is striking. Each year, fewer than 500 persons in the United States die of vaccine-preventable diseases of childhood. By comparison, 50 000 to 70 000 adults die of influenza, pneumococcal infections, and hepatitis B (Table 2).[11] In addition, many childhood vaccine-preventable infections are now found among young adults. Outbreaks of measles,[5,12] rubella,[13] and mumps[7,14] have caused major disruptions on college campuses, in the workplace, and in institutions such as hospitals and prisons. Vaccine-preventable diseases remain an important cause of costly hospitalization, especially among the elderly.[15]

Currently, 98% or more of American children are fully immunized by the time of school entry.[1] Although in some communities the proportion fully immunized by 2 years of age is much lower, several programs have been established to address this problem.[16] In contrast, and in spite of the much heavier burden of disease, vaccines that are recommended for adults are not widely used (Table 2).[11] Several reasons have been given to explain this. First, there is a limited perception on the part of both health care providers and the general public that adult vaccine-preventable diseases are significant health problems. Second, there are doubts in the minds of some health care providers and the public about the efficacy and safety of several of the vaccines used for adults. Third, adult immunization is selective not universal; different vaccines have different target groups (Table 3). Fourth, the sizes of the adult target populations for individual vaccines vary and for some vaccines are much larger than the target population for childhood vaccination. Fifth, unlike the childhood vaccination schedule that must be completed if children are to enter school, there are no statutory requirements for adult immunization. Sixth, unlike the child health care practices in most communities, there are few programs in either the public or private sectors for vaccinating adults. Finally, reimbursement for adult immunization has traditionally been neglected by both government and private insurers; children can usually obtain inexpensive or free vaccines from public health clinics, but until recently most adults have had to pay the full costs for most of their vaccines. The public availability of vaccines, school entry vaccination requirements, and responsible parenting have given our nation a high level of childhood immunization. In the best of circumstances, it would be difficult to achieve the same for adults.

In spite of these problems, adult immunization has not been ignored. More than 10 years ago two new vaccines for adults were licensed: pneumococcal vaccine in 1977 and hepatitis B vaccine in 1983. The 1980s brought many new initiatives to promote adult immunization, including those of the Advisory Committee on Immunization Practices,[16,17] the American College of Physicians,[18] the Infectious Diseases Society of America,[18] and the US Preventive Services Task Force.[19] In 1988 the Health Care Financing Administration (HCFA) launched its Medicare Influenza Vaccine Demonstration.[20] During the next 4 years, close to $69 million was spent in a multifaceted program to increase influenza vaccination among Medicare enrollees and to evaluate its cost-effectiveness and health benefits.

A complete list of committee members appears at the end of this article.

Reprint requests to National Vaccine Program Office, Rockwall II Bldg, Suite 1075, 5600 Fishers Ln, Rockville, MD 20852

Table 1.—Reported Cases of Vaccine-Preventable Childhood Diseases in the United States*

Disease	Maximal No. of Cases (y)	1993 Cases†	Reduction, %
Diphtheria	206 939 (1921)	0	−100.0
Pertussis	265 269 (1934)	6132	−97.7
Tetanus‡	1560 (1923)	9	−99.4
Poliomyelitis (paralytic)	21 269 (1952)	0§	−100.0
Measles	894 134 (1941)	277	−99.9
Rubella‖	57 686 (1969)	188	−99.7
Congenital rubella syndrome	20 000 (1964-1965)	7	−99.9
Mumps¶	152 209 (1968)	1630	−98.9

*Data from the National Immunization Program, Centers for Disease Control and Prevention (CDC), Atlanta, Ga.
†Provisional data that may change because of late reporting.
‡Data from the CDC on tetanus refer to deaths not cases; CDC does not have information on the numbers of reported tetanus cases before 1947. The number of reported deaths refers to 1992. Mortality data for 1993 are not available. The provisional number of tetanus cases reported for 1993 is 42.
§Excludes an estimated four cases of vaccine-associated paralysis.
‖Rubella first became a reportable disease in 1966.
¶Mumps first became a reportable disease in 1968.

Table 2.—Estimated Effect of Full Use of Vaccines Currently Recommended for Adults*

Disease	Estimated Annual Deaths, No.	Estimated Vaccine Efficacy, %†	Current Vaccine Utilization, %‡	Additional Preventable Deaths per y, No.§
Influenza	20 000‖	70	41	8260
Pneumococcal infection	40 000	60	20	19 200
Hepatitis B	5000	90	10¶	4050
Tetanus-diphtheria	<25	99	40#	<15
Measles, mumps, and rubella	<30	95	Variable	<30
Travelers' diseases**	<10	...††	...	<10

*Adapted from Gardner and Schaffner.[11]
†Indicates efficacy in immunocompetent adults. Among elderly and immunocompromised patients, estimated efficacy may be lower.
‡The percentage of targeted groups who have been immunized according to current recommendations. Rates vary among different targeted groups. Data for influenza and pneumococcal vaccines were obtained from the 1991 National Health Interview Survey and apply to persons 65 years of age or older.
§Calculated as follows: (potential additional vaccine utilization)×(estimated vaccine efficacy)×(estimated annual deaths).
‖Variable (range, 0 to 40 000).
¶Highly variable (range, 1% to 60%) among different targeted groups.
#This estimate is based on seroprevalence data.
**Travelers' diseases include cholera, typhoid, Japanese encephalitis, yellow fever, poliomyelitis, and rabies.
††Ellipses indicate not applicable.

Discussion of how to improve adult immunization must be included in the debate over health system reform in the United States. Vaccine-preventable diseases of adults impose significant health care costs on the nation. Yet, there is strong evidence that adult immunization is highly cost-effective.[11,18] Thus, the choice we face is not simply deciding whether to pay for adult immunization, it is whether to pay more for the costs of treating unprevented illness or less for preventing it from occurring in the first place.

In January 1994 the National Vaccine Advisory Committee (NVAC) adopted a report that reviewed the status of adult immunization in the United States.[21] This article summarizes the NVAC report, including the committee's goals and recommendations (Table 4).

1. INCREASE THE DEMAND FOR ADULT VACCINATION BY IMPROVING PROVIDER AND PUBLIC AWARENESS

In 1980 the surgeon general recommended that by 1990 60% of all elderly and high-risk persons should be immunized with influenza and pneumococcal vaccines and 50% of target groups for new vaccines (eg, hepatitis B vaccine) should be vaccinated within 5 years of vaccine licensure.[22] In 1990 these goals had not been reached.

Surveys conducted during the 1980s showed that physicians generally understood the importance of vaccine-preventable diseases and knew about the efficacy and safety of vaccines recommended for adults. However, they often failed to translate their knowledge into clinical practice.[23] Several studies demonstrated that good administration and organization were the keys to the success of vaccination programs.[23] Although specific details varied, for each successful program a decision had been made to establish an organized approach for offering vaccines to adults on a regular basis.

Better public understanding of the seriousness of vaccine-preventable diseases and the benefits of vaccination is essential.[16,18] Many elderly patients fail to appreciate that influenza presents a risk of severe illness that may lead to hospital admission or death.[23] Most elderly patients have no knowledge of the frequency or severity of pneumococcal infections. Few young adults who have multiple sexual partners understand their risks for acquiring hepatitis B. Many adults are unaware of the clinical effectiveness and safety of the vaccines that can prevent these diseases. Educational programs can help increase public understanding of the need for and benefits of adult immunization. This was illustrated recently during the HCFA Medicare Influenza Vaccine Demonstration, when a letter sent to Medicare enrollees by the HCFA administrator was helpful in persuading older persons to get vaccinated.[24]

The NVAC recommends that educational programs be undertaken to improve the adult immunization practices of physicians and other health care providers. These programs should emphasize widespread dissemination of the goals and recommendations for adult immunization, periodic assessment of provider knowledge and attitudes about vaccines and immunization practices, and better understanding of the administrative and organizational features of successful vaccination programs. Greater emphasis should be given to adult immunization in professional education and certification, and more attention should be devoted to practical approaches for vaccine delivery in training programs, including appropriate immunization of students and trainees themselves. The committee recommends that the public also be better informed of the importance of vaccine-preventable diseases of adults and of the safety and benefits of immunization. This will require an understanding of factors that constitute barriers or promote easy access to vaccination services. The committee recommends educational programs and media campaigns for adult immunization, especially those that are linked to announcements routinely directed to target populations by government agencies and community organizations.

2. ASSURE THAT THE HEALTH CARE SYSTEM HAS AN ADEQUATE CAPACITY TO DELIVER VACCINES TO ADULTS

An efficacious vaccine will be effective in preventing disease only if it is given to those who will benefit. The importance of vaccine delivery has been dramatically demonstrated by the contributions of the Centers for Disease Control and Prevention (CDC) to childhood immunization. Approximately half of all children in the United States are immunized through state and local public health programs that use vaccines purchased under federal contracts negotiated by the CDC.[1] Studies by CDC investigators on the epidemiology of vaccine-preventable diseases, the susceptibility of children to infection, and the shortcomings of vaccine delivery pro-

Table 3.—Vaccines and Toxoids Recommended for All Adults*

Age Group, y	Influenza (Annually)	Pneumococcal	Measles	Rubella	Mumps	Td†
18-24	. .	. .	X	X	X	X
25-64	. . .	. . .	X‡	X	X§	X
≥65	X	X	. . .	. .	. . .	X

*Adapted from Centers for Disease Control.[16] This report should be consulted for detailed recommendations on immunizing adults who have high-risk medical conditions, who are immunocompromised; who have special occupations, lifestyles, or environmental circumstances; or who are travelers, foreign students, immigrants, or refugees. Ellipses indicate vaccine or toxoid not universally recommended for all adults.

†Tetanus and diphtheria toxoids adsorbed (for adult use).

‡One dose of measles vaccine is indicated for persons born after 1956. A second dose is indicated for persons born after 1956 who are entering health care employment, those who are students in postsecondary educational institutions, and those who are planning international travel.

§Indicated for persons born after 1956.

grams provide the basis for the Childhood Immunization Initiative.[10] This research has shown that the majority of children and adults who develop vaccine-preventable illnesses have been seen previously by health care providers and could have been vaccinated at the time but were not.[25] Such "missed opportunities" for vaccination have several causes, including misconceptions about contraindications to vaccination and the lack of an organized approach to offering vaccines. The failure to prevent vaccine-preventable diseases is far more often due to the failure to vaccinate rather than to the failure of the vaccines themselves. The costs of these "missed opportunities" are very high.

Most vaccines given to adults are administered by generalist physicians, yet wide variations have been shown in their immunization practices.[18,22] Many adults who should be vaccinated receive their principal care from specialists rather than general physicians or from highly specialized teams of health care professionals or administrative units such as clinics. In such settings, a single focus of responsibility for offering vaccines is often difficult to identify. Thus, efforts to improve adult immunization must focus on developing workable systems for regularly offering vaccines to patients at risk, regardless of where they receive their care. Such systems should reflect practice guidelines, and their evaluation should become a common feature of quality assurance and accreditation programs.

The NVAC recommends that the CDC and other federal agencies assume increased responsibility for assuring that adults are appropriately immunized. This will require support for vaccine purchase and program administration at the state and local levels, as well as increased staff and support at the CDC itself. The committee urges that all health care providers, whether generalists or specialists, consider any contact with adult patients as an opportunity to provide recommended vaccines. The committee recommends that health care providers and the institutions in which they practice adopt administrative and organizational arrangements that guarantee the regular offering of vaccines to adults, develop and implement standards and practice guidelines for adult immunization, and include regular evaluation of immunization practices as part of their quality assurance programs.

3. ASSURE ADEQUATE FINANCING MECHANISMS TO SUPPORT THE EXPANDED DELIVERY OF VACCINES TO ADULTS

Childhood immunization programs have long received financial support from federal, state, and local governments. Public agencies have been much less involved with adult immunization; in 1991 less than 10% of all doses of influenza and pneumococcal vaccines used in the United States were given by state and local health departments (CDC, unpublished data, 1993). To address this problem, in 1981 the Congress instructed the HCFA to pay physicians for pneumococcal vaccination of elderly patients under Part B of the Medicare program.[23] In 1984 reimbursement for hepatitis B vaccination was added for Medicare patients with end-stage renal disease. In 1993 Medicare was authorized to pay for influenza vaccine and its administration.[21]

The implementation of Medicare reimbursement for vaccination has not measured up to its promise. For example, Medicare reimbursement for pneumococcal vaccination during the 1980s barely covered the cost of the vaccine alone.[23] Each year during the period 1985 through 1988, only 300 000 to 400 000 doses of pneumococcal vaccine—25% of all doses distributed nationwide—could be accounted for by the Medicare reimbursement program. Whether adequate reimbursement is important for adult immunization should become apparent in Medicare's recently established program to pay for annual influenza vaccination.

There is little information on the extent to which private health insurance companies provide coverage for adult immunization. Health maintenance organizations may provide such services, but their immunization rates are often no better than those of patients covered by traditional health insurance.[26] Reliance on regulatory approaches to improve private health insurance coverage of adult immunization may not be sufficient; businesses that self-insure their employees are not subject to regulation by state governments. Proposals for health system reform usually include coverage of childhood immunization. Similar coverage is needed for adult immunization.

The NVAC recommends that publicly funded health insurance programs adequately reimburse providers for the costs of vaccines and their administration to adults. Medicare and Medicaid reimbursement policies must be monitored to ensure that they are effectively implemented by fiscal intermediaries and providers alike. When problems are identified, technical assistance must be provided and financial or other incentives considered so that adults enrolled in these programs are appropriately immunized. Similarly, the committee recommends that private health insurance companies adequately reimburse providers for adult immunization, without requiring individual co-payments or deductibles. Business and labor leaders and state health insurance regulators should encourage inclusion of adult immunization as a cov-

Table 4.—The National Vaccine Advisory Committee's Goals and Recommendations for Adult Immunization*

1. Increase the demand for adult vaccination by improving provider and public awareness
   - Conduct effective information programs for
     - Health care providers to improve their immunization practices
     - The public to emphasize the importance of vaccine-preventable diseases and the safety and benefits of immunization
2. Assure the health care system has an adequate capacity to deliver vaccines to adults
   - Establish an adult immunization grant program to assist state and local health departments
   - Reduce missed opportunities for vaccination
   - Appropriately vaccinate adult patients in
     - Primary care settings
     - Specialty practices and institutions
   - Implement guidelines and standards for adult immunization practice
3. Assure adequate financial mechanisms to support the expanded provision of vaccines to adults
   - Adequately reimburse providers through
     - Publicly funded programs such as Medicare and Medicaid
     - Private health insurance
   - Include coverage for adult immunization in national health system reform
4. Monitor and improve the performance of the nation's vaccine delivery system
   - Expand programs for disease surveillance
   - Preserve and strengthen vaccine-manufacturing capacity to meet the nation's needs
   - Endeavor to achieve the adult immunization goals of *Healthy People 2000*
5. Assure adequate support for research
   - Support research on
     - Adult vaccine-preventabe diseases
     - Efficacy, safety, clinical effectiveness, and cost-benefit/cost-effectiveness of adult immunization
     - Epidemiology of adult immunization practices
     - New and improved vaccines
     - International programs for adult immunization

*From National Vaccine Advisory Committee.[7]

ered benefit for those insured. Finally, the committee strongly recommends that all national health system reform proposals include coverage for adult immunization services and provide mechanisms to finance their delivery.

4. MONITOR AND IMPROVE THE PERFORMANCE OF THE NATION'S VACCINE DELIVERY SYSTEM

The nation's ability to control vaccine-preventable diseases requires continuing surveillance of the diseases themselves, an assured manufacturing capacity to provide the vaccines needed, and periodic assessment of whether the vaccines are reaching the persons for whom they are intended.

The effective and efficient use of vaccines in adults depends on a clear understanding of which diseases are epidemiologically important and which persons are at risk of infection. The CDC works closely with state and local health departments to monitor the occurrence of vaccine-preventable diseases. For example, it regularly provides timely advice on the identity of influenza viruses causing outbreaks and information on whether the current influenza vaccine should be protective.[27] Surveillance by the CDC has provided better understanding of the epidemiology of hepatitis B[28] and pneumococcal infections.[29] These programs could be improved if inexpensive methods were developed for more rapid diagnosis of disease. Surveillance is also essential for accurately assessing the economic impact of vaccine-preventable diseases.

The success of our nation's immunization programs depends on the capacity of our vaccine manufacturers to produce and distribute a constant supply of vaccine products. During the swine influenza program in 1976, our system for vaccine supply was severely tested.[30] In the 1960s liability costs contributed to the rise in prices for childhood vaccines and seriously threatened the economic viability of vaccine manufacturers.[31] The National Vaccine Injury Compensation Program, established in 1986, provides a mechanism by which claims for childhood vaccine-associated injuries can now be settled.[32] Although its implementation has been costly and not without problems, the program has succeeded in stabilizing the market for the vaccine manufacturers.

One reason why the 1990 goals for adult immunization were not reached may be the failure to monitor adult immunization practices. In 1989 the National Center for Health Statistics began to gather better information on vaccination levels against influenza, pneumococcal disease, tetanus, and diphtheria. Its National Health Interview Survey has shown, for example, that only 20% of elderly persons have ever received pneumococcal vaccine.[33] However, little is known about geographic variations in the use of this vaccine or about vaccination rates in persons at increased risk of disease. For hepatitis B vaccine, a great deal is known about vaccination status of health care workers, but almost nothing is known about the status of the other high-risk groups that account for more than 96% of all cases of the disease.[28]

The NVAC recommends that surveillance of vaccine-preventable diseases by the CDC and by state and local health agencies be strengthened, including the development of better methods of diagnosing disease. The committee recommends that the capacity of the nation's vaccine manufacturers to meet current and future needs for vaccines be periodically assessed to identify potential technical, regulatory, financial, legal, or political problems that could threaten adequate supplies of vaccines for adult immunization. This assessment should also determine the appropriate level of federal involvement in vaccine purchase, production, and compensation for vaccine-related adverse events. To reach the adult immunization goals of *Healthy People 2000*, the committee recommends more detailed evaluation of vaccination levels in adults with specific high-risk conditions and in specific population groups at risk. It also recommends support for programs to improve vaccine delivery where immunization rates are found to be unsatisfactory. (The adult immunization goals of *Healthy People 2000* provide for increases in immunization levels as follows: (1) pneumococcal pneumonia and influenza immunization among institutionalized chronically ill or older people to at least 80%; (2) pneumococcal pneumonia and influenza immunization among noninstitutionalized, high-risk populations as defined by the Advisory Committee on Immunization Practices to at least 60%; and (3) hepatitis B immunization among high-risk populations, including infants of surface antigen–positive mothers, to at least 90%; occupationally exposed workers to at least 90%; intravenous-drug users in drug treatment programs to at least 50%; and homosexual men to at least 50%.)

5. ASSURE ADEQUATE SUPPORT FOR RESEARCH

Basic research on the viruses and bacteria that cause disease is essential if we are to develop new and improved vaccines.[34] Equally important is research on host responses to infection and vaccination, especially the responses of older adults whose immune systems become less responsive with advancing age. For each vaccine, initial evaluation of its efficacy must be followed by an assessment of its clinical effectiveness in preventing the more serious and costly outcomes of disease. In addition, much more needs to be known about the health and economic consequences of vaccine-preventable diseases. The cost-effectiveness of adult immunization must be further assessed; current evidence suggests that influenza and pneumococcal vaccination are highly cost-effective when compared with other preventive, screening, and treatment interventions in common use among elderly persons.[35] New knowledge about the epidemiology of vaccine-preventable diseases must be accompanied by research on the epidemiology of efforts to prevent these diseases, including variations in the vaccination practices of health care providers. The importance of this research is illustrated by a recent study showing that persons at greatest risk of influenza were least likely to be vaccinated.[23]

Research has provided several new and improved vaccines that may benefit adults, including cold-adapted live influenza, pneumococcal conjugate, varicella-zoster, hepatitis A, and acellular pertussis vaccines.[14,24] Promising new methods of vaccine administration are being developed, including newer adjuvants, epitope-based strategies that reflect an understanding of antigen recognition sites, particulate antigens delivered as microcapsules, glycoconjugate preparations, immunologic boosting with cytokines and lymphokines, and the use of vaccine vectors.

Whether adults in the United States are to be protected against vaccine-preventable diseases will depend to some extent on the occurrence of these diseases in other parts of the world. Current international programs for monitoring diseases such as influenza need to be supplemented by surveillance programs for other emerging and reemerging infectious diseases, such as diphtheria in countries of the former Soviet Union,[36] a new strain of *Vibrio cholerae* in South Asia,[37] and the spread of antimicrobial-resistant *Streptococcus pneumoniae* in many countries.[27] International disease surveillance and vaccination programs have already paid rich dividends in the worldwide eradication of smallpox and the elimination of poliomyelitis in the Americas. Given the promise of new and improved vaccines, the Children's Vaccine Initiative has become the organizing focus to coordinate the transfer of new technologies for vaccine production and vaccine delivery to developing countries.[38] Many aspects of this program have direct implications for the development of new and improved vaccines for adults.

The NVAC recommends continued support of research on the microbiology-

cal agents of and the host response to vaccine-preventable infections, including those of immunocompromised and aging individuals. The committee urges the development of better measures of the health and economic consequences of current and future vaccine-preventable diseases. The committee recognizes that the viability of our nation's adult immunization programs requires continued evidence of the efficacy, effectiveness, safety, and cost-effectiveness of current and future vaccines. The committee recommends greater attention be given to studies of the epidemiology of immunization practices. Research on new and improved vaccines for use in the United States and internationally must be assured stable and continuing support. Finally, the committee encourages greater collaboration between federal agencies, nongovernmental organizations, professional associations, and vaccine companies in the United States and their counterparts in international organizations and in countries throughout the world.

CONCLUSION

In making its recommendations, the NVAC recognizes that none of its goals for adult immunization will be reached without giving attention to all. The task is complex and the effort and resources needed to achieve success will be substantial. However, in undertaking this work, the committee is reminded that our nation's programs for childhood immunization have reduced the costs of health care and improved the well-being of all our children. We can and should expect no less from our efforts to immunize adults.

The National Vaccine Program was established in 1986 by the Public Health Service Act to achieve optimal prevention of infectious disease through immunization and optimal prevention of adverse reactions to vaccines. The program is responsible for coordination and direction of government and nongovernment activities on research, licensing, production, distribution, and use of vaccines. The director is the assistant secretary for health, with the National Vaccine Advisory Committee serving as advisor. The committee consists of 16 voting members appointed by the director, in consultation with the National Academy of Sciences, including individuals in vaccine research or manufacture, physicians, members of parent organizations, and representatives of health agencies and public health organizations. The committee also includes five nonvoting members from the National Institutes of Health, the Food and Drug Administration, the Centers for Disease Control and Prevention, the Agency for International Development, and the Department of Defense.

Members of the National Vaccine Advisory Committee are as follows:

Vincent A. Fulginiti, MD (*Chair*), University of Colorado Health Science Center, Denver; Barry R. Bloom, PhD, Albert Einstein College of Medicine, Bronx, NY; Judy Braiman, Empire State Consumer Association, Rochester, NY; Betty F. Bumpers, Every Child By Two, Washington, DC; Robert B. Couch, MD, Baylor College of Medicine, Houston, Tex; R. Gordon Douglas, Jr, MD, Merck & Co Inc, Whitehouse Station, NJ; David S. Fedson, MD, University of Virginia Medical Center, Charlottesville; Charles M. Helms, MD, PhD, University of Iowa, Iowa City; Paul P. Hung, PhD, Wyeth-Ayerst Laboratories, Philadelphia, Pa; Kay Johnson, The March of Dimes, Washington, DC; David T. Karzon, MD, Vanderbilt University School of Medicine, Nashville, Tenn; Susan M. Lett, MD, MPH, Massachusetts Department of Public Health, Jamaica Plain; Robert K. Ross, MD, Department of Health Services, San Diego, Calif; Daniel W. Shea, MD, DePere, Wis; Sylvia F. Villarreal, MD, University of California–San Francisco.

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APPENDIX I
Immunization Resources

Appendix I

Centers for Disease Control and Prevention
and
National Immunization Program

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, or to find the location of immunization clinics near you, or to order single copies of immunization materials from NIP.

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 National Immunization Program expert, usually within 24 hours.

Internet

NIP: http://www.cdc.gov/nip
Hepatitis: http://www.cdc.gov/hepatitis
Influenza: http://www.cdc.gov/flu
Travelers' Health: http://www.cdc.gov/travel

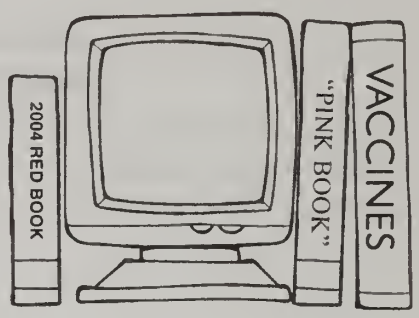
Calendar of upcoming events, online access to publications such as ACIP statements and Vaccine Information Statements, online publications ordering, vaccine safety information, latest pediatric and adult immunization schedules, downloadable Clinic Assessment Software Application (CASA), Frequently Asked Questions, PowerPoint slide presentations from the Pink Book and from NIP satellite broadcasts, links to other immunization sites, and much more.

NIP Training & Education Resources. Download NIP's curriculum brochure:
http://www.cdc.gov/nip/ed/curriculum/curric-brochure.htm

Publications may be ordered through NIP's online order form:
http://www.cdc.gov/nip/publications

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 Subscriptions:** Information about how to sign up to receive periodic email updates from several immunization-related organizations.
- **Hotlines:** Information about toll-free hotlines for providers and patients.
- **International Organizations:** Links to organizations (e.g., WHO, PAHO, GAVI) providing information on global and international immunization and hepatitis issues.

Visit us:

www.immunize.org/resources

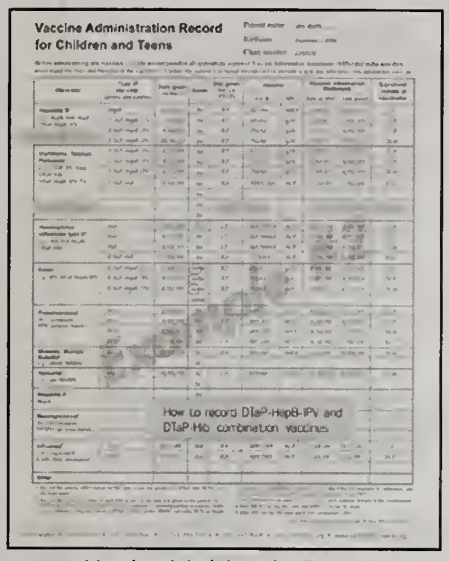
- **IAC Materials:** Links to IAC's ready-to-print educational pieces for providers, patients, and parents — and much more.
- **Other Immunization Partners:** Links to other organizations and professional societies that provide immunization information.
- **State and Federal Agencies and Programs:** Links to most federal agencies (e.g., CDC, FDA) and state health departments.
- **Videos:** Helpful videos for providers, patients, and parents to learn more about immunization and viral hepatitis.

www.immunize.org/news.d/6012resr.pdf • Item #U6012 (12/04)

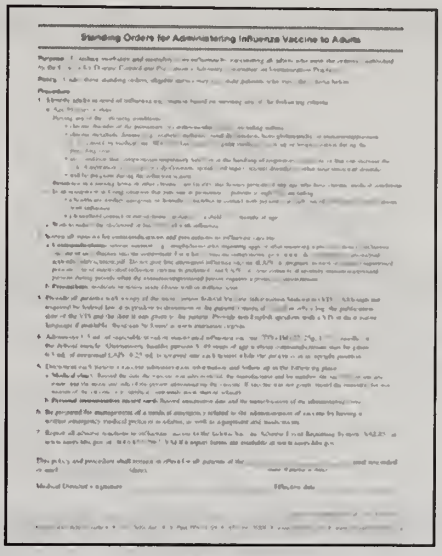
Immunization Action Coalition • 1573 Selby Avenue • St. Paul, MN 55104 • (651) 647-9009 • www.immunize.org

Sample IAC Print Materials

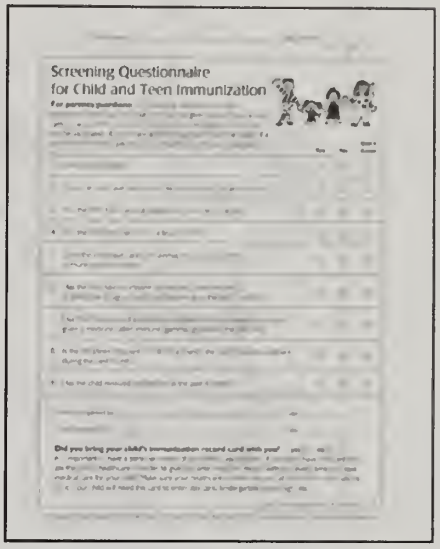
These, and many other useful materials for both providers and patients, can be downloaded free of charge from the IAC's website at http://www.immunize.org/catg.d/free.htm



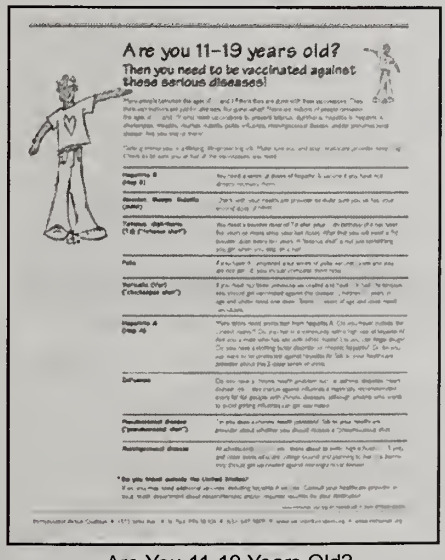
Vaccine AdministrationRecord
for Children and Teens
http://www.immunize.org/catg.d/p2022b.pdf



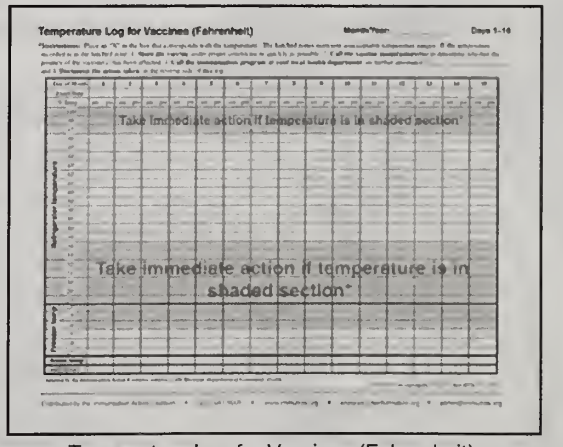
Standing Orders for Administering
Influenza Vaccine to Adults
http://www.immunize.org/catg.d/p3074.pdf



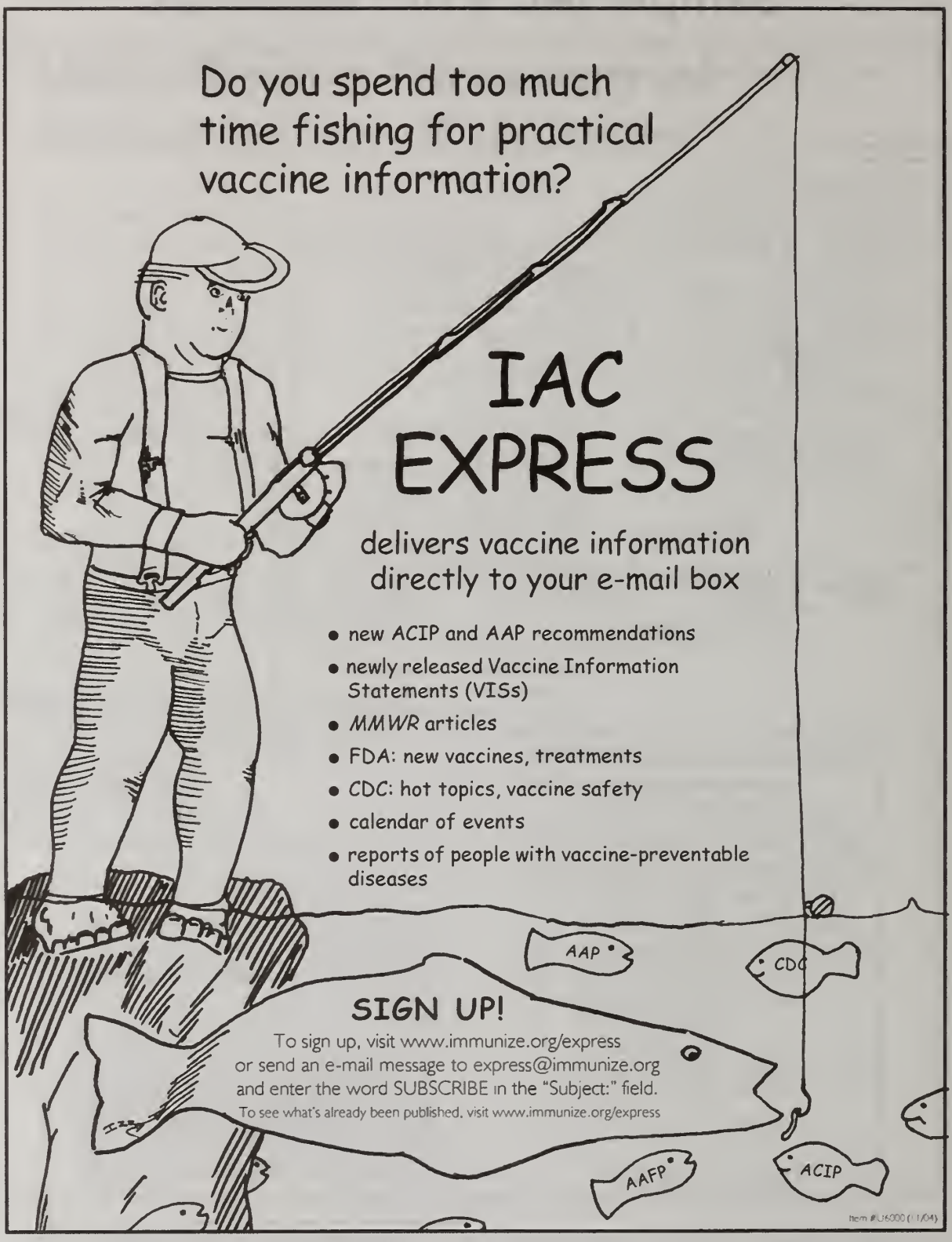
Screening Questionnaire
for Child and Teen Immunization
http://www.immunize.org/catg.d/p4060scr.pdf



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



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This award winning 35-minute program, by the California Department of Health Services Immunization Branch, includes the latest information on injection techniques for immunizing children and adults. Available on VHS and DVD. DVD includes English and Spanish versions plus resources. This program can be ordered by fax or online at www.cdlhn.com.

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City:_____ State:_____ Zip:_____

Telephone: (_____)_____ E-mail:_____

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IMM-712	Immunization Techniques Video: 1-10 copies @ $30.00 ea ☐ Eng. ☐ Span.		$30.00 each	
IMM-712	Immunization Techniques Video: 11-100 copies @ $25.00 ea ☐ Eng. ☐ Span.		$25.00 each	
IMM-712	Immunization Techniques Video: 101+ copies @ $20.00 ea ☐ Eng. ☐ Span.		$20.00 each	
IMM-712 DVD	Immunization Techniques DVD: English & Spanish		$35.00 each	
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Other immunization related products:

IMM-674	Immunization Techniques - Comfort Measures Poster		$20/set of 5	
IMM-720	Immunization Techniques - Comforting Restraint Double-sided Flyer		$2 each	
IMM-712	Immunization Techniques - Comfort Measures English/Spanish Take Home Flyer		$10/tablet of 50	
IMM-686	Immunization Techniques - Anatomic Sites		$20/set of 5	
IMM-721	Immunization Techniques - Print Material Artwork		$50	

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Global Vaccination Information

Statistics and Graphics

(http://www.who.int/immunization_monitoring/data/en/)

This page contains links to slides, maps, tables, and other documents relating to global and national disease incidence, vaccine coverage, and other immunization-related topics.

Global Summary "Country Profile Selection Centre"

(http://www-nt.who.int/immunization_monitoring/en/globalsummary/countryprofileselect.cfm)

On this page the reader can view an "Immunization Profile" for a selected country, which includes information on population, disease incidence, vaccine coverage, and the routine schedule.

NATIONAL IMMUNIZATION PROGRAM
IMMUNIZATION GRANTEES
December 13, 2005

STATE & CITY GRANTEES

ALABAMA
Alabama Department of Public Health
State Immunization Program
P.O. Box 303017
Montgomery, AL 36130-3017
Fed Ex: Disease Control/Immunization Div.
The RSA Tower
201 Monroe St., Suite 1460
Montgomery, AL 36104

PHONE #: (334) 206-5023
FAX #: (334) 206-2044
Program Manager: Winkler Sims
Email: wsims@adph.state.al.us

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: Laural 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: Kathy Fredrickson
Email: Fredrik@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: Charles Beets
Email: cbeets@healthyarkansas.com

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: Howard Backer
Email: Hbacker@dhs.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: Rebecca Jordan
Email: rebecca.jordan@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@po.state.ct.us

DELAWARE
Immunization Program/Div of Public Health
Delaware Dept of Health & Social Services
The Jessie Cooper Building
Federal & Water Street
Dover, Delaware 19901

PHONE #: (302) 741-2940
FAX #: (302) 739-2358
ProgramManager: Martin Luta
Email: martin.luta@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., 15th Floor, Rm 470
Atlanta, Georgia 30303

PHONE #: (404) 657-3158
FAX #: (404) 657-1463
Program Manager: Michael Chaney
Email: mechaney@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: Malama Markowitz
Email: ralene.m.markowitz@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: Tricia Hosch-Hebdon
Email: hoscht@idhw.state.id.us

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: Kmcmahon@idph.state.il.us

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: Maribel Chavez-Torres
Email: Chavez-Torres_M@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: Carol Briley
Email: cbriley@isdh.IN.govs

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: Michael Runau
Email: mrunau@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:

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: RAT1017@yahoo.com

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: Pejman Talebian
Email: Pejman.Talebian@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: Kristin Ehressmann
Email: Kristen.Ehresmann@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: Joy Sennett (acting)
Email: jsennett@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: Brad Hall
Email: hallb@dhss.state.mo.us

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: Joyce Burgett
Email: jburgett@state.mt.us

NEBRASKA
Nebraska Department of Health & Human Services
Immunization Program
301 Centennial Mall South
P.O. Box 95044
Lincoln, Nebraska 68509-5044

PHONE #: (402) 471-6423
FAX #: (402) 471-6426
Program Manager: Barbara Ludwig
Email: barbara.ludwig@hhss.ne.gov

NEVADA
Nevada State Health Division
Immunization Program
505 King Street
Carson City, Nevada 89710

PHONE #: (775) 684-5900
FAX #: (775) 684-8338
Program Manager: Bob Salcido
Email: bsalcido@nvhd.state.nv.us

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: Michael Dumond
Email: mdumond@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: Kate Wytovich
Email: Katherine.Wytovich@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: Steve Nickell
Email: steveni@doh.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: Heather Weaver
Email: hweaver@state.nd.us

OHIO
Ohio Department of Health
Immunization Program
35 East Chestnut - 7th Floor
Columbus, Ohio 43215

PHONE #: (614) 466-4643
FAX #: (614) 728-4279
Program Manager: Tony Payton
Email: Tpayton@odh.ohio.gov

OKLAHOMA
Oklahoma State Department of Health
Immunization Program - 0306
1000 N.E. 10th Street
Oklahoma City, Oklahoma 73117-1299

PHONE #: (405) 271-4073
FAX #: (405) 271-6133
Program Manager: Don Blose
Email: donb@health.state.ok.us

OREGON
Oregon Immunization Program
800 NE Oregon Street
Suite 370
Portland, Oregon 97232

PHONE #: (503) 731-4020
FAX #: (503) 731-3095
Program Manager: Lorraine Duncan
Email: Lorraine.Duncan@state.or.us

PENNSYLVANIA
Pennsylvania Department of Health
Division of Immunizations
Rm 1026 Health & Welfare Bldg
Commonwealth & Forrester St.
Harrisburg, Pennsylvania 17120

PHONE #: (717) 787-5681
FAX #: (717) 705-5513
Program Manager: Alice Gray
Email: agray@state.pa.us

PHILADELPHIA
Philadelphia Department of Health
Division of Disease Control
500 South Broad Street
Philadelphia, Pennsylvania 19146
PHONE #: (215) 685-6748
FAX #: (215) 685-6806
Program Manager: Andrew Chilkatowsky
Email: andrew.chilkatowsky@phila.gov

RHODE ISLAND
Rhode Island Department of Health
mmunization Program
3 Capital Hill - Room 302
Providence, Rhode Island 02908-5097
PHONE #: (401) 222-2312
FAX #: (401) 222-1442
Program Manager: Becky Bessette
Email: BeckyB@doh.state.ri.us

SOUTH CAROLINA
South Carolina Department of Health
and Environmental Control
Immunization Division
1751 Calhoun Street
Columbia, South Carolina 29201
PHONE #: (803) 898-0460
FAX #: (803) 898-0318
Program Manager: Jesse Greene
Email: greeneje@dhec.sc.us

SOUTH DAKOTA
South Dakota Department of Health
615 East 4th Street
Pierre, South Dakota 57501
PHONE #: (605) 773-5323
FAX #: (605) 773-5509
Program Manager: Michelle Hudacek
Email: michelle.hudecek@state.sd.us

TENNESSEE
Tennessee Department of Health
Immunization Program
Cordell Hull Building, 4th Floor
425 5th Avenue North
Nashville, Tennessee 37247-4911
PHONE #: (615) 741-7247
FAX #: (615) 741-3857
Program Manager: Pamelia Baggett
Email: Pamelia.baggett@state.tn.us

TEXAS
Texas Department of Health
Immunization Division
1100 West 49th Street
Austin, Texas 78756
PHONE #: (512) 458-7284
FAX #: (512) 458-7288
Program Manager: Jack Sims
Email: Jack.sims@dshs.state.tx.us

HOUSTON
Houston Health & Human Services Dept
Immunization Bureau
8000 North Stadium Drive
Houston, Texas 77054
PHONE #: (713) 794-9267
FAX #: (713) 794-9937
Program Manager: Risha Jones
Email: Risha.Jones@cityofhouston.net

SAN ANTONIO
San Antonio Metro Health District
Immunization Division
332 West Commerce Street, Suite 202
San Antonio, Texas 78205
PHONE #: (210) 207-8790
FAX #: (210) 207-8882
Program Manager: Brenda Lemke
Email: BrendaL@sanantonio.gov

UTAH
Utah Department of Health
CFHS/Immunization
P.O. Box 142001
Salt Lake City, Utah 84114-2001
PHONE #: (801) 538-9450
FAX #: (801) 538-9440
Program Manager: Linda Abel
Email: lable@utah.gov

VERMONT
Vermont Department of Health
Immunization Program
P.O. Box 70
108 Cherry Street
Burlington, Vermont 05402

PHONE #: (802) 863-7638
FAX #: (802) 865-7701
Program Manager: Sue Barry
Email: sbarry@vdh.state.vt.us

VIRGINIA
Virginia State Department of Health
Division of Immunization
1500 E. Main Street - Room 120
Richmond, Virginia 23219

PHONE #: (804) 864-8055
FAX #: (804) 786-0396
Program Manager: Jim Farrell
Email: jfarrell@vdh.virginia.gov

WASHINGTON
Washington State Department of Health
Office of Immunization
Newmarket Industrial Campus
P.O. Box 47843
Olympia, Washington 98504-7843
Fed Ex: DOH/Immunization Program
Newmarket Industrial Campus Bldg 1
7171 Cleanwater Lane
Olympia, WA 98501

PHONE #: (360) 236-3595
FAX #: (360) 235-3590
Program Manager: Janna Bardi
Email: jjanna.bardi@doh.wa.gov

WASHINGTON, DC
Department of Public Health
Preventive Hlth Svcs Administration
Division of Immunization
1131 Spring Road, N.W.
Washington, DC 20010

PHONE #: (202) 576-7130
FAX #: (202) 576-6418
Program Manager: Rosie McLaren
Email: Rmclaren@dc.gov

WEST VIRGINIA
West Virginia Department of Health & Human Resources
Bureau for Public Health
Immunization Program
350 Capitol Street, Rm 125
Charleston, West Virginia 25301-3715

PHONE #: (304) 558-2188
FAX #: (304) 558-1941
Program Manager: Jeff Neccuzi
jeffneccuzi@wvdhhr.org

WISCONSIN
Wisconsin Division of Public Health
Immunization Program
1 West Wilson St, Rm 318
P.O. Box 2659
Madison, Wisconsin 53702-2659

PHONE #: (608) 267-9959
FAX #: (608) 267-9493
Program Manager: Dan Hopfensperger
Email: hopfedj@dhfs.state.wi.us

WYOMING
Wyoming Division of Health
Community and Family Health Div.
Hathaway Building, Room 424
2300 Capitol Ave
Cheyenne, Wyoming 82002

PHONE #: (307) 777-7942
FAX #: (307) 777-6001
Program Manager: Katelyn Wells-Fahling
Email: kfahli@state.wy.us

Appendix I

OTHER GRANTEES

AMERICAN SAMOA
Department of Health, IM Program
Division of Public Health
Government of American Samoa
LBJ Tropical Medical Center
Pago Pago, AS 96799

PHONE #: 011-684-633-7223
FAX #: 011-684-633-5379
Program Manager: Joseph Tufa
Email: yt_masunu@hotmail.com

GUAM
Department of Public Health and Social Services
Immunization Program
123 Chalan Kareta, Route 10
Mangilao, Guam 96923

PHONE #: 011-671-735-7143
FAX #: 011-671-734-1475
Program Manager: JosieO'Mallan
Email: JTOMallan@dphss.govguam.net

INDIAN HEALTH SERVICE
Indian Health Services HQ West
Epidemiology Department - 3rd Floor
5300 Homestead Rd., N.E.
Albuquerque, New Mexico 87110

PHONE #: (505) 248-4226
FAX #: (505) 248-4393
Program Manager: Amy Groom
Email: amy.groom@mail.ihs.gov

MARSHALL ISLANDS
Republic of the Marshall Islands
Ministry of Health Services
Immunization Program
P.O. Box 16
Majuro, Marshall Island 96960

PHONE #: 011-692-625-8457
FAX #: 011-692-625-3432
Program Manager: Mailynn Konelios
Email: phadmin@ntamar.net

MICRONESIA
Federated States of Micronesia
Division of Health Services
Immunization Program
P.O. Box PS 70, Palikir
Ponape, FM 96941

PHONE #: 011-691-320-2619
FAX #: 011-691-320-5263
Program Manager: Louisa Helgenberger
Email: lahelgenberger@mail.fm

NORTHERN MARIANA ISLANDS
Department of Public Health & Environmental Service
Commonwealth Health Center
Lower Navy Hill
P.O. Box 409
Saipan, N. Mariana Is. 96950

PHONE #: 011-670-236-8733
FAX #: 011-670-234-8930
Program Manager: Mariana Sablan
Email: mariana@gtepacifica.net

PALAU
Bureau of Health Services
Immunization Program
Republic of Palau
Belau National Hosp Building
Koror, RP 96940

PHONE #: 011-680-488-4804
FAX #: 011-680-488-3115
Program Manager: Ann Klass
Email: phpal@palaunet.com

PUERTO RICO
Puerto Rico Department of Health
Immunization Program
Program for Communicable Diseases
P.A.S.E.T., Box 70184
San Juan, Puerto Rico 00936
Fed Ex: Dept. De Salud, Edificio A
Antigua Hosp de Psiquiatria
Pabellon #1, Primer Piso
Seccion de Vacunacion
Rio Piedras, Puerto Rico 00922

PHONE #: (787) 274-5612
FAX #: (787) 274-5619
Program Manager: Angel Rivera
Email: anrivera@salud.gov.pr

VIRGIN ISLANDS
Virgin Islands Department of Health
Roy L. Schneider Hospital
Immunization Program
48 Sugar Estate
St. Thomas, Virgin Islands 00802

PHONE #: (340) 776-8311 ext. 2151
FAX #: (340) 777-8762
Program Manager: Joan Montenegro
Email: immunize@viaccess.net

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION