Epidemiology and Prevention of Vaccine-Preventable Diseases



10th EDITION

Department of Health and Human Services
Centers for Disease Control and Prevention
Safer • Healthier • People™

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Epidemiology and Prevention of Vaccine Preventable Diseases
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Latest Entry: 7/20/07

ERRATUM
Chapter 14: Hepatitis A
The last paragraph on page 198 begins, "IgM anti-HAV appears in the convalescent phase . . ." It should read, "IgG anti-HAV appears . . ." This has been corrected in the online version of the chapter. (7/20/07)

ERRATUM
Chapter 20: Rotavirus
On page 301, both the text (3rd pagagraph under "Vaccination Schedule and Use") and the middle slide state that rotavirus vaccine should not be administered "on or after age 32 weeks." This should read "on or after age 33 weeks." In other words, the vaccine may be administered *through* the 32nd week of age. (5/15/07)

UPDATE
Appendix B
Hungarian has been added to the languages included on Table 1 of Foreign Language Terms (4/9/07)

UPDATE
Chapter 14: Hepatitis A & Chapter 15: Hepatitis B
The U.S. Food and Drug Administration (FDA) has approved Twinrix® [Hepatitis A Vaccine (Inactivated) and Hepatitis B (Recombinant) Vaccine], for an accelerated dosing schedule that consists of three doses given within three weeks followed by a booster dose at 12 months. The approval means Twinrix is now available on a dosing schedule at 0, 7, 21-30 days, followed by a booster dose at 12 months. The vaccine was first approved for adults over age 18 years by the FDA in May 2001 on a 0, 1, 6-month dosing schedule. **NOTE:** The 4-day grace period for minimum intervals **cannot** be applied to this schedule. (4/3/07)

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- **Chapter 1**. **Principles of Vaccination** (downloads/prinvac.pdf) (295KB)
- **Chapter 2**. **General Recommendations on Immunization** (downloads/genrec.pdf) (528KB)
- **Chapter 3**. **Immunization Strategies** (downloads/strat.pdf) (330KB)
- **Chapter 4**. **Vaccine Safety** (downloads/safety.pdf) (352KB)
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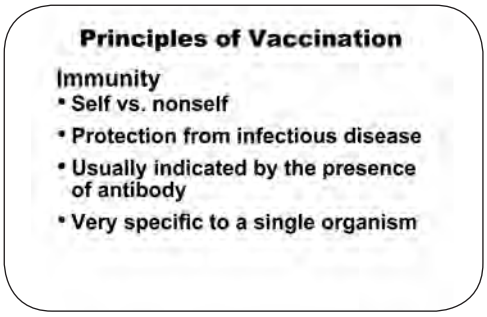
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Principles of Vaccination

Immunology and Vaccine-Preventable Diseases

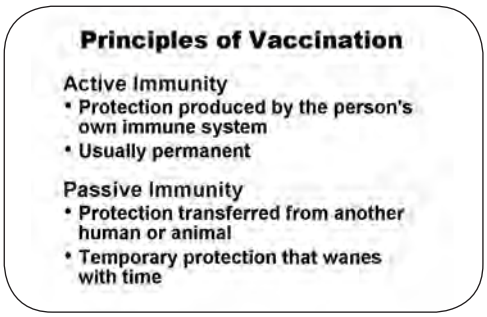
Immunology is a complicated subject, and a detailed discussion of it is beyond the scope of this text. However, an understanding of the basic function of the immune system is useful in order to understand both how vaccines work and the basis of recommendations for their use. The description that follows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

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

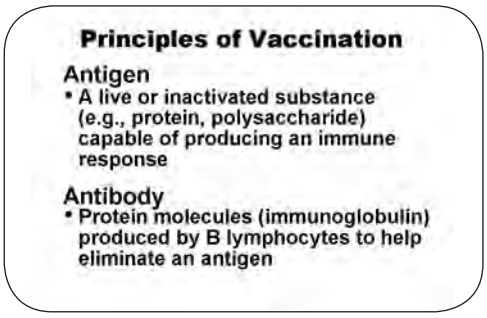


Active immunity is protection that is produced by the person's own immune system. This type of immunity is usually permanent.

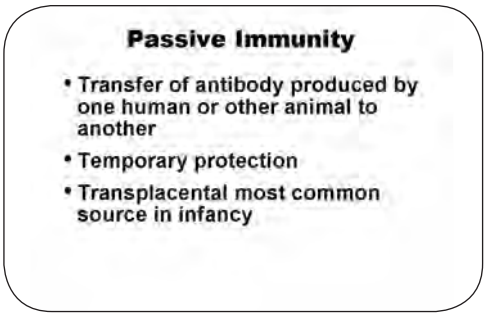
Passive immunity is protection by products produced by an animal or human and transferred to another human, usually by injection. Passive immunity often provides effective protection, but this protection wanes (disappears) with time, usually within a few weeks or months.

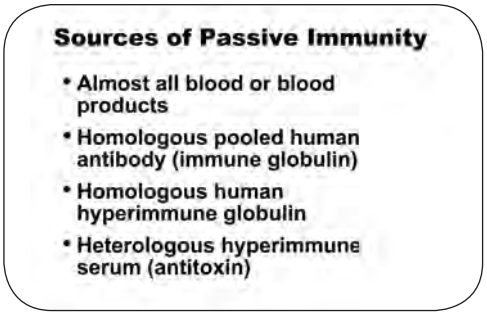


The immune system is a complex system of interacting cells whose primary purpose is to identify foreign ("nonself") substances referred to as antigens. Antigens can be either live (such as viruses and bacteria) or inactivated. The immune system develops a defense against the antigen. This defense is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



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





Passive Immunity

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

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

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

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

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

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

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

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

Monoclonal Antibody

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

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

Antibody for Prevention of RSV

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

Active Immunity

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

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

Vaccination

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

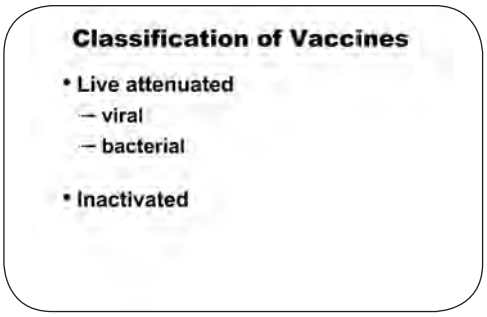
Another way to produce active immunity is by vaccination. Vaccines interact with the immune system and often produce an immune response similar to that produced by the natural infection, but they do not subject the recipient to the disease and its potential complications. Many vaccines also produce immunologic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

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

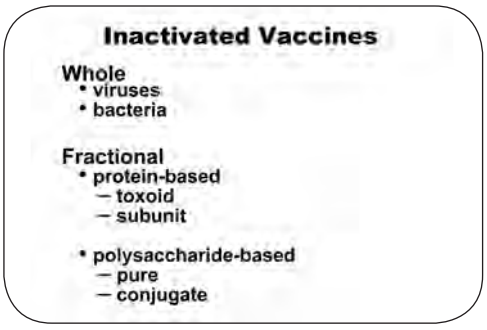
added to improve the immunogenicity of the vaccine). Host factors such as age, nutritional factors, genetics, and coexisting disease, may also affect the response.

Classification of Vaccines

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



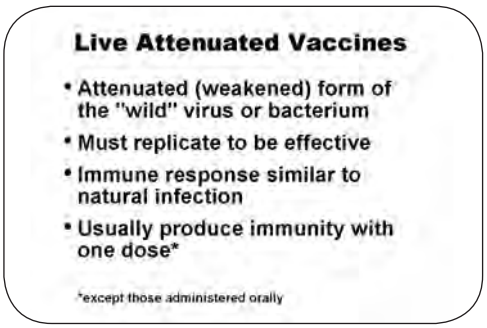
Live attenuated vaccines are produced by modifying a disease-producing ("wild") virus or bacterium in a laboratory. The resulting vaccine organism retains the ability to replicate (grow) and produce immunity, but usually does not cause illness. The majority of live attenuated vaccines available in the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



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

GENERAL RULE

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



Live Attenuated Vaccines

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

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

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

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

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

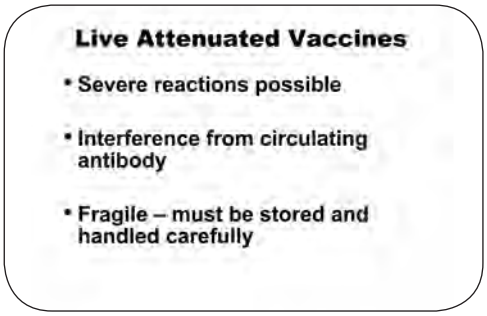
Live attenuated vaccines may cause severe or fatal reactions as a result of uncontrolled replication (growth) of the vaccine virus. This only occurs in persons with immunodeficiency (e.g., from leukemia, treatment with certain drugs, or human immunodeficiency virus (HIV) infection).

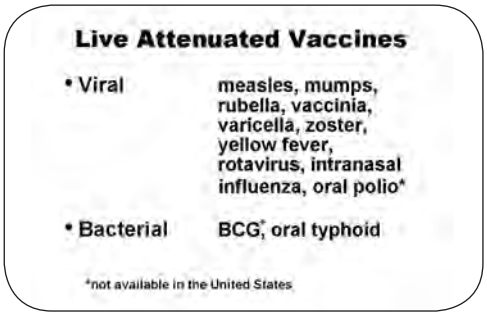
A live attenuated vaccine virus could theoretically revert to its original pathogenic (disease-causing) form. This is known to happen only with live (oral) polio vaccine.

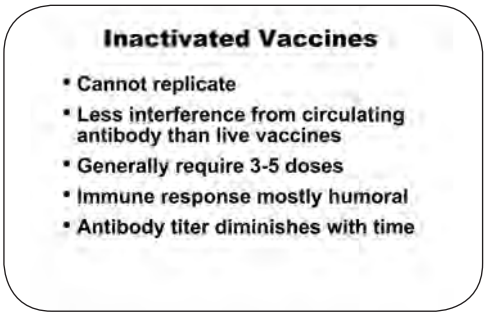
Active immunity from a live attenuated vaccine may not develop because of interference from circulating antibody to the vaccine virus. Antibody from any source (e.g., transplacental, transfusion) can interfere with replication of the vaccine organism and lead to poor response or no response to the vaccine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

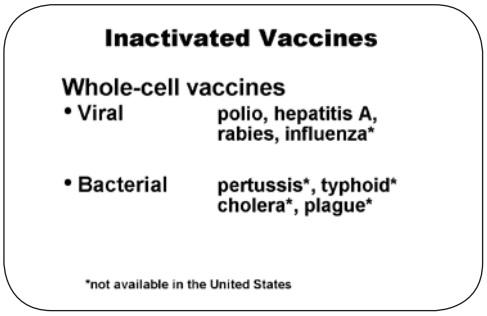
Live attenuated vaccines are fragile and can be damaged or destroyed by heat and light. They must be handled and stored carefully.

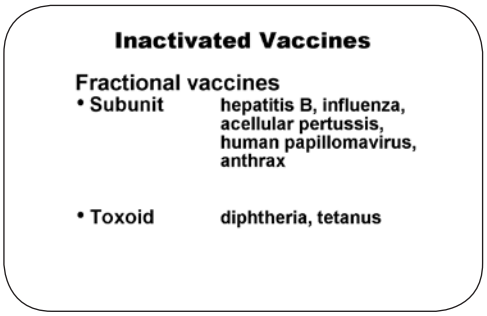
Currently available live attenuated viral vaccines are measles, mumps, rubella, vaccinia, varicella, zoster (which contains the same virus as varicella vaccine but in much higher amount), yellow fever, rotavirus, and influenza (intranasal). Oral polio vaccine is a live viral vaccine but is no longer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

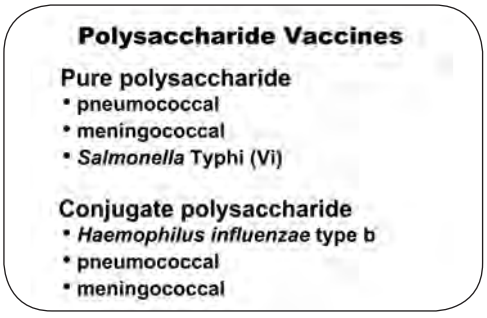












Inactivated Vaccines

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

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

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

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

Polysaccharide Vaccines

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

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

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

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

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

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

Pure Polysaccharide Vaccines

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

Recombinant Vaccines

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

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

Principles of Vaccination

1

General Recommendations on Immunization

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

Timing and Spacing of Vaccines

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

Antibody–Vaccine Interactions

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.

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

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

Antibody and Live Vaccines

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

*except rotavirus vaccine, which should be delayed for 6 weeks, if possible

Live Injected Vaccines

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

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

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

Live Oral and Intranasal Vaccines

Available data suggest that the presence of passive antibody may reduce or blunt the response to live oral rotavirus vaccine. The Advisory Committee on Immunization Practices

(ACIP) recommends deferral of rotavirus vaccination for 6 weeks after receipt of a blood product if possible. However, if the 6-week deferral would cause the first dose of rotavirus vaccine to be scheduled for 13 weeks of age or older, a shorter deferral interval should be used to ensure the first dose is administered before age 13 weeks.

Oral typhoid and yellow fever vaccines are not known to be affected by the administration of immune globulin or blood products. This is because few North Americans are immune to yellow fever or typhoid. Consequently, donated blood products in the United States do not contain a significant amount of antibody to these organisms. Typhoid and yellow fever vaccines may be given simultaneously with blood products, or separated by any interval. The replication of live attenuated influenza vaccine (LAIV) is not believed to be affected by antibody-containing blood products. LAIV can be given any time before, during or after administration of antibody-containing blood products.

Products Containing Type-Specific or Negligible Antibody

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

Products Containing Type-Specific or Negligible Antibody

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

Simultaneous and Nonsimultaneous Administration

GENERAL RULE

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

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

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

Spacing of Vaccine Combinations Not Given Simultaneously

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

Spacing of Live Vaccines not Given Simultaneously

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

Nonsimultaneous Administration of Different Vaccines

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

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

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

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

Interval Between Doses of the Same Vaccine

GENERAL RULE

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

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

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

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

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

Minimum Intervals and Ages

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

Violation of Minimum Intervals or Minimum Age

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

Extended Interval Between Doses

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

(e.g., habitually misses appointments), it may be preferable to administer the vaccine at that visit than to reschedule a later appointment that may not be kept.

Vaccine doses administered up to 4 days before the minimum interval or age can be counted as valid. This 4-day recommendation does not apply to rabies vaccine because of the unique schedule for this vaccine. Doses administered 5 days or earlier than the minimum interval or age should not be counted as valid doses and should be repeated as age appropriate. The repeat dose should generally be spaced after the invalid dose by an interval at least equal to the recommended minimum interval shown in Table 1 of the General Recommendations. In certain situations, local or state requirements might mandate that doses of selected vaccines be administered on or after specific ages, superseding this 4-day "grace period."

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

Number of Doses

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

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

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

Adverse Reactions Following Vaccination

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

Vaccine Adverse Reactions

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

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

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

Vaccine Adverse Reactions

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

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

Vaccine Adverse Reactions

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

Systemic adverse reactions were relatively frequent with DTP vaccine, which contained a whole-cell pertussis com-

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
  - rare
  - risk minimized by screening

ponent. However, comparison of the frequency of systemic adverse events among vaccine and placebo recipients shows they are less common with inactivated vaccines currently in use, including acellular pertussis vaccine.

Systemic adverse reactions may occur following receipt of live attenuated vaccines. Live attenuated vaccines must replicate in order to produce immunity. The adverse reactions that follow live attenuated vaccines, such as fever or rash, represent symptoms produced from viral replication and are similar to a mild form of the natural disease. Systemic adverse reactions following live vaccines are usually mild, and occur 7–21 days after the vaccine was given (i.e., after an incubation period of the vaccine virus). LAIV replicates in the mucous membranes of the nose and throat, not in the lung. As a result, LAIV may cause upper respiratory symptoms (like a cold) but not influenza-like symptoms.

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

Reporting Vaccine Adverse Events

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

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

Contraindications and Precautions to Vaccination

Contraindications and precautions to vaccination generally dictate circumstances when vaccines will not be given. Most

contraindications and precautions are temporary, and the vaccine can be given at a later time.

A contraindication is a condition in a recipient that greatly increases the chance of a serious adverse reaction. It is a condition in the recipient of the vaccine, not with the vaccine per se. If the vaccine were given in the presence of that condition, the resulting adverse reaction could seriously harm the recipient. For instance, administering influenza vaccine to a person with a true anaphylactic allergy to egg could cause serious illness or death in the recipient. In general, vaccines should not be administered when a contraindication condition is present.

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

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

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

Contraindication

- A condition in a recipient that greatly 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
- Might compromise the ability of the vaccine to produce immunity

Contraindications and Precautions

Permanent contraindications to vaccination:

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

Contraindications and Precautions

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

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

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

Allergy

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

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

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

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

Latex is sap from the commercial rubber tree. Latex contains naturally occurring impurities (e.g., plant proteins and peptides),

which are believed to be responsible for allergic reactions. Latex is processed to form natural rubber latex and dry natural rubber. Dry natural rubber and natural rubber latex might contain the same plant impurities as latex but in lesser amounts. Natural rubber latex is used to produce medical gloves, catheters, and other products. Dry natural rubber is used in syringe plungers, vial stoppers, and injection ports on intravascular tubing. Synthetic rubber and synthetic latex also are used in medical gloves, syringe plungers, and vial stoppers. Synthetic rubber and synthetic latex do not contain natural rubber or natural latex, and therefore, do not contain the impurities linked to allergic reactions.

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

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

Pregnancy

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

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

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

Vaccination of Pregnant Women

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

Use of Tdap Among Pregnant Women*

- Any woman who might become pregnant is encouraged to receive a single dose of Tdap
- Women who have not received Tdap should receive a dose in the immediate postpartum period
- ACIP recommends Td when tetanus and diphtheria protection is required during pregnancy
- Pregnancy is not a contraindication for Tdap
- Clinician may choose to administer Tdap to a pregnant woman in certain circumstances (such as during a community pertussis outbreak)

*Provisional recommendations approved by ACIP June 28, 2006

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

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

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

Vaccination of Immunosuppressed Persons

- Live vaccines should not be administered to severely immunosuppressed persons
- Persons with isolated B-cell deficiency may receive varicella vaccine
- Inactivated vaccines are safe to use in immunosuppressed persons but the response to the vaccine may be decreased

Immunosuppression

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

Immunosuppression

- Disease
  - —congenital immunodeficiency
  - —leukemia or lymphoma
  - —generalized malignancy
- Chemotherapy
  - —alkylating agents
  - —antimetabolites
  - —radiation

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. Household contacts of immunosuppressed persons may receive zoster vaccine if indicated. Transmission has not been documented from a person who received herpes zoster vaccine.

Certain drugs may cause immunosuppression. For instance, persons receiving cancer treatment with alkylating agents

or antimetabolites, or radiation therapy should not be given live vaccines. Live vaccines can be given after chemotherapy has been discontinued for at least 3 months. Persons receiving large doses of corticosteroids should not receive live vaccines. For example, this would include persons receiving 20 milligrams or more of prednisone daily or 2 or more milligrams of prednisone per kilogram of body weight per day for 14 days or longer.

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

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

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

Immunosuppression

- Corticosteroids
  - —20 mg or more per day of prednisone*
  - —2 mg/kg or more per day of prednisone*
  - —NOT aerosols, alternate-day, short courses, topical

*for 14 days or longer

HIV Infection

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

Live Attenuated Vaccines for Persons with HIV/AIDS*

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

Yes=vaccinate No=do not vaccinate

*see specific ACIP recommendations for details.
+children only.

Varicella and measles can be very severe illnesses in persons with HIV infection and are often associated with complications. Varicella vaccine is recommended for children (but not adults) with HIV infection who are not severely immunosuppressed. Zoster vaccine should not be given to persons with AIDS or clinical manifestations of HIV infection. Measles vaccine (as combination MMR vaccine) is recommended for persons with HIV infection who are asymptomatic or mildly immunosuppressed. However, persons with severe immunosuppression due to HIV infection should not receive measles vaccine or MMR. MMRV should not be administered to persons with HIV infection. Persons with HIV infection should not receive LAIV; they should receive inactivated influenza vaccine (TIV). Data are insufficient from clinical trials to support administration of rotavirus vaccine to infants with indeterminant HIV status who are born to mothers with HIV/AIDS. Yellow fever vaccine should be considered for persons who do not have AIDS or other symptomatic manifestations of HIV infection, who have established laboratory verification of adequate immune system function, and who cannot avoid potential exposure to yellow fever virus.

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

Vaccination of Hematopoietic Stem Cell Transplant Recipients

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

Vaccination of Hematopoietic Stem Cell Transplant Recipients

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

MMWR 2000;49(RR-10)

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

especially if the HSCT recipient is younger than 60 months. Two doses of PCV followed by a dose of pneumococcal polysaccharide vaccine (at least 8 weeks after the second dose of PCV) are recommended.

MMR and varicella vaccines should be administered 24 months after transplantation if the HSCT recipient is presumed to be immunocompetent. Meningococcal vaccines are not currently recommended for HSCT recipients because of insufficient experience using these vaccines among HSCT recipients.

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

Vaccination of Hematopoietic Stem Cell Transplant Recipients

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

MMWR 2000;49(RR-10) and *MMWR* 2006;55(RR-15)

Moderate or Severe Acute Illness

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

Invalid Contraindications to Vaccination

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

Invalid Contraindications to Vaccination

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

Mild Illness

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

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

Antimicrobial Therapy

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

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

Disease Exposure or Convalescence

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

Pregnant or Immunosuppressed Person in the Household

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

Measles and mumps vaccine viruses produce a noncommunicable infection and are not transmitted to household contacts. Rubella vaccine virus has been shown to be shed in human milk, but transmission to an infant has rarely been documented. Transmission of varicella vaccine virus is not common, and most women and older immunosuppressed persons are immune from having had chickenpox as a child. Transmission of zoster vaccine virus to household or other close contacts has not been reported.

Breastfeeding

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

Preterm Birth

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

Studies demonstrate that decreased seroconversion rates might occur among preterm infants with very low birth weight (less than 2,000 grams) after administration of hepatitis B vaccine at birth. However, by 1 month chronological age, all preterm infants, regardless of initial birth weight or gestational age are as likely to respond as adequately as older and larger infants. All preterm infants born to hepatitis B surface antigen (HBsAg)–positive mothers and mothers with unknown HBsAg status must receive immunoprophylaxis with hepatitis B vaccine and hepatitis B immunoglobulin (HBIG) within 12 hours after birth. If these infants weigh less than 2000 grams at birth, the initial vaccine dose should not be counted toward completion of the hepatitis B vaccine series, and three additional doses of hepatitis B vaccine should be administered beginning when the infant is 1 month of age.

Preterm infants with a birth weight of less than 2000 grams who are born to women documented to be HBsAg-negative at the time of birth should receive the first dose of the hepatitis B vaccine series at 1 month of chronological age or at the time of hospital discharge.

Allergy to Products Not Present in Vaccine

Infants and children with nonspecific allergies, duck or feather allergy, or allergy to penicillin, children who have relatives with allergies, and children taking allergy shots can and should be immunized. No vaccine available in the United States contains duck antigen or penicillin.

Allergy That is Not Anaphylactic

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

Family History of Adverse Events

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

Tuberculin Skin Test

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

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

Multiple Vaccines

As noted earlier in this chapter, administration at the same visit of all vaccines for which a person is eligible is critical

to reaching and maintaining high vaccination coverage. All vaccines (except vaccinia) can be administered at the same visit as all other vaccines.

Screening for Contraindications and Precautions to Vaccination

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

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

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

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

Screening Questions

- Is the child (or are you) sick today?
- Does the child have allergies to medications, food, or any vaccine?
- Has the child had a serious reaction to a vaccine in the past?
- Has the child had a seizure, or brain or nerve problem?
- Does the child have cancer, leukemia, AIDS, or any other immune system problem?

Screening Questions

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

pertussis outbreak). A local reaction (redness or swelling at the site of injection) is not a contraindication to subsequent doses.

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

A history of Guillain-Barré syndrome (GBS) is a consideration with the following vaccines:

- Td/Tdap. If GBS has occurred within 6 weeks of a tetanus-containing vaccine and the decision is made to continue vaccination, give age-appropriate Tdap instead of Td if there is no history of prior Tdap.
- Inactivated influenza vaccine (TIV). If GBS has occurred within 6 weeks of prior TIV, vaccinate with TIV if the person is at high risk for severe influenza complications.
- LAIV. If GBS history is present, do not give LAIV.
- MCV4. Avoid vaccinating unless the person is in a recommended risk group.

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

Has the child taken cortisone, prednisone, other steroids, or anticancer drugs, or had x-ray treatments in the past 3 months?
Live-virus vaccines (e.g., MMR, varicella, zoster, LAIV) should be postponed until after chemotherapy or long-term, high-dose steroid therapy has ended. Details and the length of time to postpone vaccination are described elsewhere in this chapter and in the *General Recommendations on Immunization*.

Has the child received a transfusion of blood or blood products, or been given a medicine called immune (gamma) globulin in the past year?
Certain live virus vaccines (e.g., MMR, varicella, rotavirus) may need to be deferred, depending on the type of blood product and the interval since the blood product was administered. Information on recommended intervals between immune globulin or blood product administration and MMR or varicella vaccination is in Appendix A and in the *General Recommendations on Immunization*.

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

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

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

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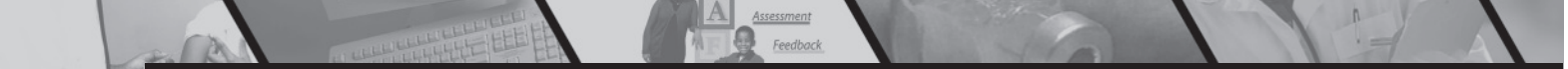
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Immunization Strategies for Healthcare Practices and Providers

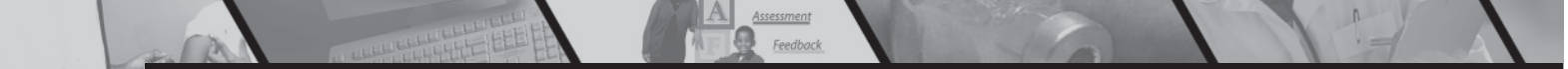
The Need for Strategies to Increase Immunization Levels

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 2004, only 37 cases of measles, 10 cases of rubella, no cases of diphtheria, 34 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.



Immunization Strategies for Healthcare Practices and Providers

The Need for Strategies to Increase Immunization Levels

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

Childhood immunization rates are still suboptimal. In 2005, for example, only 85.7% of children 19 to 35 months of age had received four doses of DTaP vaccine.

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

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

Uptake is lagging for some antigens. In 2005, for example, the percentage of children who had received varicella vaccine by their second birthday was 87.9%. 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.

Why Focus on Strategies to Increase Immunization?

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

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

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

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

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

One key to a successful strategy to increase immunization is matching the proposed solution to the current problem. At present in the United States, most persons have sufficient interest in and access to health care and are seen, at least periodically, in healthcare systems. Those who remain unvaccinated are so largely because healthcare practices and providers do not always optimally perform the activities associated with delivering vaccines and keeping patients up-to-date with their immunization schedules. Although a combination of strategies—directed at both providers and the public—is necessary for increasing and maintaining high immunization rates, this chapter focuses on immunization strategies for healthcare practices and providers.

The AFIX Approach

The 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

Special Characteristics of AFIX

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

it attempt to persuade clients to be vaccinated, but instead focuses on changing healthcare provider behavior. Third, AFIX, when used successfully, is a unique blend of advanced technology and personal interaction. Much of the AFIX 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 have been successful with other providers, the more knowledgeable and

eXchange of Information

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

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.

Comprehensive Clinic Assessment Software Application (CoCASA)

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

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).

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

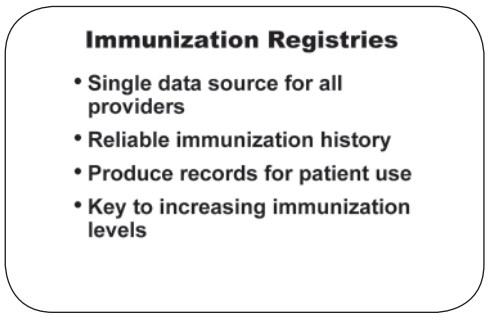
- Must be available at the time of the visit
- Must be easy to read
- Must be accurate
  - —reflect current patient population
  - —reflect all vaccines given

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

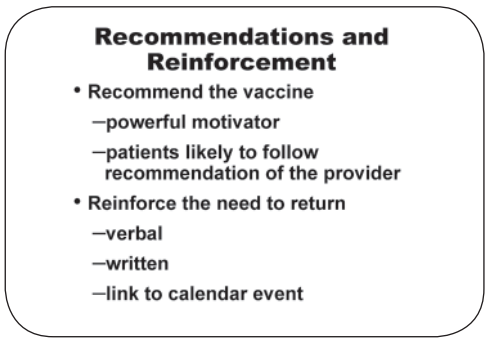
Many recordkeeping tasks, as well as patient reminder/recall activities, can be greatly simplified by participation in a population-based immunization registry, also known as an immunization information system. An immunization registry is a computerized information system that contains information about 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.



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 provider's practice, or by the child's age or geographic area. A goal of *Healthy People 2010* is to increase to 95% the proportion of children younger than 6 years of age who participate in fully operational, population-based immunization registries. In 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.



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 Opportunity

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

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

Reasons for Missed Opportunities

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

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

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

Strategies for Reducing Missed Opportunities

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

- Standing orders. These are protocols whereby nonphysician immunization personnel may vaccinate clients without direct physician involvement at the time of the immunization. Standing orders are implemented in settings such as clinics, hospitals, and nursing homes. When used alone or in combination with other interventions, standing orders have had positive effects on immunization rates among adults.

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

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

Reduction to Barriers to Immunization

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

Reduction of Barriers to Immunization Within the Practice

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.

Acknowledgments

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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.

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

Decreases in Disease Risks

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

Public Confidence

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

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

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

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

Sound Immunization Recommendations and Policy

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

Importance of Vaccine Safety

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

Methods of Monitoring Vaccine Safety

Prelicensure

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

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

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

Prelicensure Vaccine Safety Studies

- Laboratory
- Animals
- Humans

Prelicensure Human Studies

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

Postlicensure Surveillance

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

Postlicensure Vaccine Safety Activities

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

Vaccine Adverse Event Reporting System (VAERS)

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

Vaccine Adverse Event Reporting System (VAERS)

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

Postlicensure

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

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

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

The Vaccine Adverse Event Reporting System

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

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

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

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

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

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

Adverse Event Classifications and Assessment of Causality

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

Adverse Event Classification

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

Vaccine adverse events can be classified as follows:

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

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

Vaccine Safety Datalink (VSD)

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

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

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

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

Vaccine Safety Datalink (VSD)

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

Clinical Immunization Safety Assessment Network

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

Clinical Immunization Safety Assessment (CISA) Network

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

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

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

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

Vaccine Injury Compensation

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

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

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

The 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.

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

Contraindication

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

Precaution

A condition in a recipient that might

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

Invalid Contraindications to Vaccination

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

Contraindications and Precautions

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

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

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

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

Managing Vaccine Side Effects

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

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**

Reporting Suspected Side Effects to VAERS

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

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

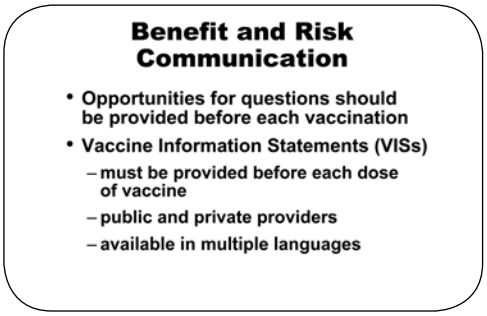
  VAERS
  P.O. Box 1100
  Rockville, MD 20849-1100

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

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

Benefit and Risk Communication

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



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

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

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

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

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

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

Acknowlegements

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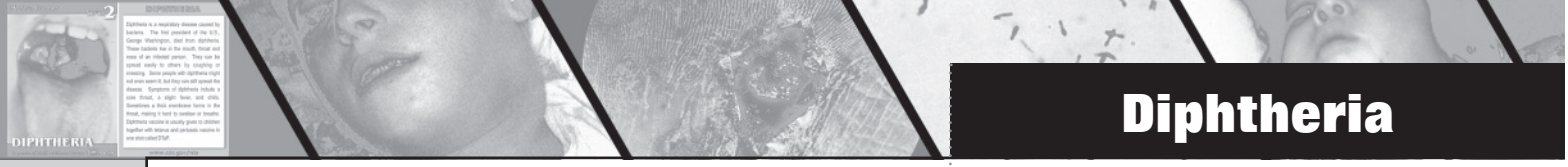
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Diphtheria

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

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

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.

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

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

Epidemiology

Occurrence

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

Diphtheria Epidemiology

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

Reservoir

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

Transmission

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

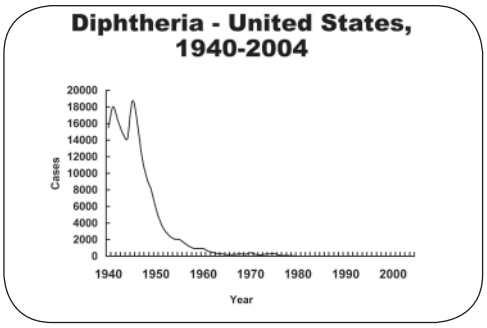
Diphtheria

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.

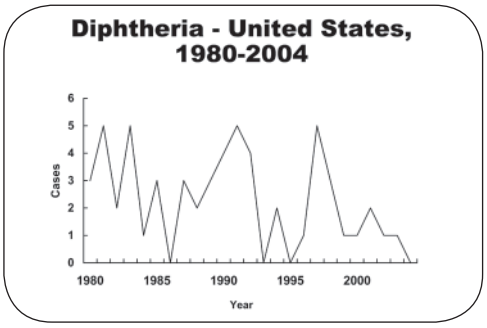


Secular Trends in the United States

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.

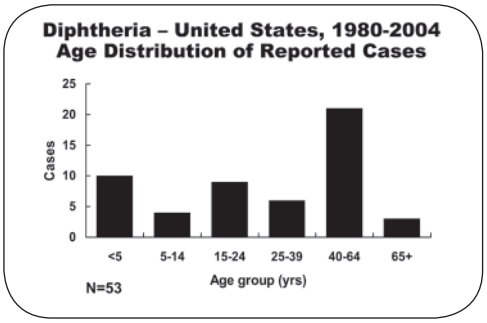
In the 1920s in the United States, 100,000–200,000 cases of diphtheria (140–150 cases per 100,000 population) and 13,000–15,000 deaths were reported each year. In 1921, a total of 206,000 cases and 15,520 deaths were reported. The number of cases gradually declined to about 19,000 cases in 1945 (15 per 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, Td and Tdap

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

DTaP and pediatric DT used through age 6 years. Adult Td for persons 7 years and older. Tdap for persons 10-18 years (Boostrix) or 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

Routine DTaP Primary Vaccination Schedule

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

Children Who Receive DT

- The number of doses of DT needed to complete the series depends on the child's age at the first dose:
  - —if first dose given at <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 Younger Than 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 and Older

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

Booster dose every 10 years

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

Immunogenicity and Vaccine Efficacy

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

Vaccination Schedule and Use

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

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

If the fourth dose of DT, DTP or DTaP is administered before the fourth birthday, a booster (fifth) dose is recommended at 4–6 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.

Diphtheria and Tetanus Toxoids Adverse Reactions

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

Exaggerated local (Arthus-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.

Contraindications and Precautions to Vaccination

Persons with a history of a severe allergic reaction to a vaccine component or following a prior dose should not receive additional doses of diphtheria toxoid. Diphtheria toxoid

Diphtheria and Tetanus Toxoids Contraindications and Precautions

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

should be deferred for those persons who have moderate or severe acute illness, but persons with minor illness may be vaccinated. Immunosuppression and pregnancy are not contraindications to receiving diphtheria toxoid. See pertussis chapter for additional information on contraindications and precautions to Tdap.

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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Diphtheria

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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

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 more than 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

Occurrence

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

Tetanus Epidemiology

• Reservoir	Soil and intestine of animals and humans
• Transmission	Contaminated wounds Tissue injury
• Temporal pattern	Peak in summer or wet season
• Communicability	Not contagious

Reservoir

Organisms are found primarily in the soil and intestinal tracts of animals and humans.

Mode of Transmission

Transmission is primarily by contaminated wounds (apparent and inapparent). The wound may be major or minor. In recent years, however, a higher proportion of patients had minor wounds, probably because severe wounds are more likely to be properly managed. Tetanus may follow elective surgery, burns, deep puncture wounds, crush wounds, otitis media (ear infections), dental infection, animal bites, abortion, and pregnancy.

Communicability

Tetanus is not contagious from person to person. It is the only vaccine-preventable disease that is infectious but not contagious.

Secular Trends in the United States

A marked decrease in mortality from tetanus occurred from the early 1900s to the late 1940s. In the late 1940s, tetanus toxoid was introduced into routine childhood immunization and tetanus became nationally notifiable. At that time, 500–600 cases (approximately 0.4 cases per 100,000 population) were reported per year.

After the 1940s, reported tetanus incidence rates declined steadily. Since the mid-1970s, 50–100 cases (~0.05 cases per 100,000) have been reported annually. 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.

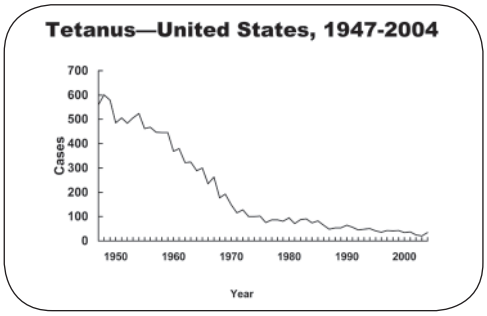
From 1980 through 2000, 70% of reported cases of tetanus were among persons 40 years of age or older. From 1980 through 1990, a median of 21% of reported cases were among persons younger than 40 years of age. The age distribution of reported cases shifted to a younger age group in the last half of the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

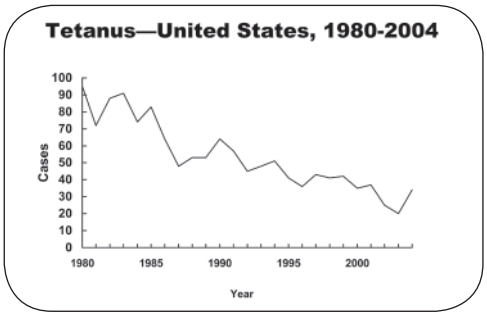
Almost all reported cases of tetanus are in persons who have either never been vaccinated, or who completed a primary series but have not had a booster in the preceding 10 years.

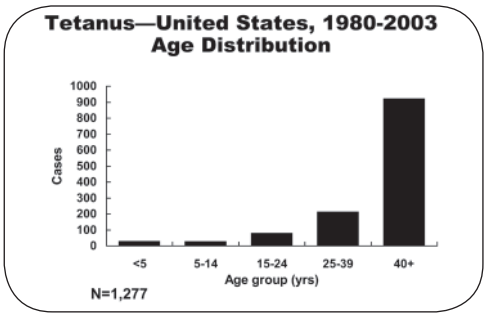
Heroin users, particularly persons who inject themselves subcutaneously, appear to be at high risk for tetanus. Quinine is used to dilute heroin and may support the growth of C. *tetani*.

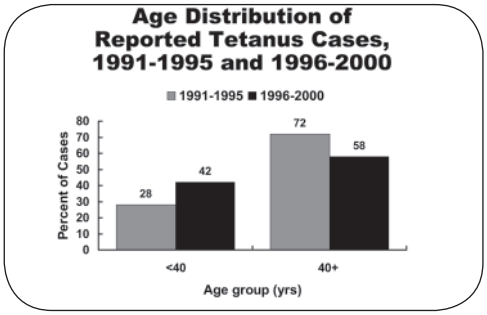
Neonatal tetanus is rare in the United States, with only two cases reported since 1989. Neither of the infants' mothers had ever received tetanus toxoid.

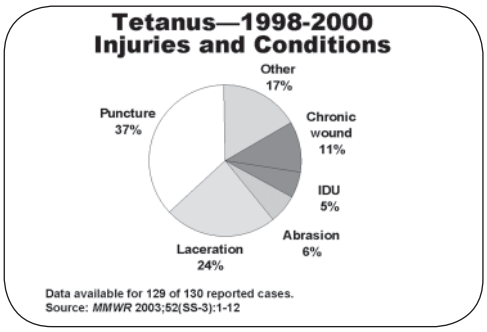
During 1998–2000 (the most recent years for which data are available), acute injuries or wounds preceded tetanus in 94 (73%) of the 129 cases for which information was available. Among the most frequent wound types were puncture wounds (50%), lacerations (33%), and abrasions (9%). The most common puncture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

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

DTaP and pediatric DT used through age 6 years. Adult Td for persons 7 years and older. Tdap for persons 10-18 years (Boostrix) or 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 weeks
Primary 3	6 months	4 weeks
Primary 4	15-18 months	6 months

Children Who Receive DT

- The number of doses of DT needed to complete the series depends on the child's age at the first dose:
  - —if first dose given at <12 months of age, 4 doses are recommended
  - —if first dose given at ≥12 months, 3 doses complete the primary series

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.

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)

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.

Routine Td Schedule
Unvaccinated Persons ≥7 Years of Age

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

Booster dose every 10 years

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

Diphtheria and Tetanus Toxoids
Adverse Reactions

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

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.

Diphtheria and Tetanus Toxoids Contraindications and Precautions

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

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.

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 294,000 deaths resulting from the disease in 2002 (World Health Organization estimate).

Pertussis

- Highly contagious respiratory infection caused by *Bordetella pertussis*
- Outbreaks first described in 16th century
- *Bordetella pertussis* isolated in 1906
- Estimated 294,000 deaths worldwide in 2002

Bordetella pertussis

B. pertussis is a small, aerobic gram-negative rod. It is fastidious and requires special media for isolation (see Laboratory Diagnosis).

B. pertussis produces multiple antigenic and biologically active products, including pertussis toxin, filamentous hemagglutinin, agglutinogens, adenylate cyclase, pertactin, and tracheal cytotoxin. These products are responsible for the clinical features of pertussis disease, and an immune response to one or more produces immunity following infection. Immunity following *B. pertussis* infection does not appear to be permanent.

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 cilia of the respiratory epithelial cells, produce toxins that paralyze the cilia, and cause inflammation of the respiratory tract, which interferes with the clearing of pulmonary secretions. Pertussis antigens appear to allow the organism to evade host defenses, in that lymphocytosis is promoted but chemotaxis is impaired. Until recently it was thought that *B. pertussis* did not invade the tissues. However, recent studies have shown the bacteria to be present in alveolar macrophages.

Pertussis Pathogenesis

- Primarily a toxin-mediated disease
- Bacteria attach to cilia of respiratory epithelial cells
- Inflammation occurs which interferes with clearance of pulmonary secretions
- Pertussis antigens allow evasion of host defenses (lymphocytosis promoted but impaired chemotaxis)

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 Clinical Features

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

Pertussis Among Adolescents and Adults

- Disease often milder than in infants and children
- Infection may be asymptomatic, or may present as classic pertussis
- Persons with mild disease may transmit the infection
- Older persons often source of infection for children

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)

The first stage, the catarrhal stage, is characterized by the insidious onset of coryza (runny nose), sneezing, low-grade fever, and a mild, occasional cough, similar to the common cold. The cough gradually becomes more severe, and after 1–2 weeks, the second, or paroxysmal stage, begins. Fever is generally minimal throughout the course of the illness.

It is during the paroxysmal stage that the diagnosis of pertussis is usually suspected. Characteristically, the patient has bursts, or paroxysms, of numerous, rapid coughs, apparently due to difficulty expelling thick mucus from the tracheobronchial tree. At the end of the paroxysm, a long inspiratory effort is usually accompanied by a characteristic high-pitched whoop. During such an attack, the patient may become cyanotic (turn blue). Children and young infants, especially, appear very ill and distressed. Vomiting and exhaustion commonly follow the episode. The person does not appear to be ill between attacks.

Paroxysmal attacks occur more frequently at night, with an average of 15 attacks per 24 hours. During the first 1 or 2 weeks of this stage, the attacks increase in frequency, remain at the same level for 2 to 3 weeks, and then gradually decrease. The paroxysmal stage usually lasts 1 to 6 weeks but may persist for up to 10 weeks. Infants younger than 6 months of age may not have the strength to have a whoop, but they do have paroxysms of coughing.

In the convalescent stage, recovery is gradual. The cough becomes less paroxysmal and disappears in 2 to 3 weeks. However, paroxysms often recur with subsequent respiratory infections for many months after the onset of pertussis.

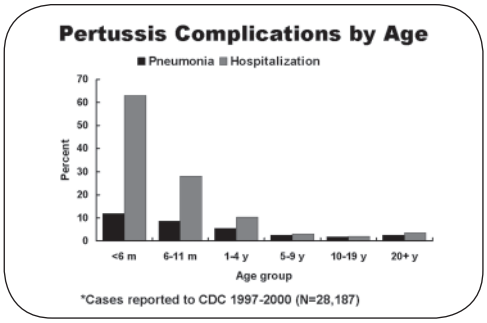
Adolescents and adults and children partially protected by the vaccine may become infected with *B. pertussis* but may have milder disease than infants and young children. Pertussis infection in these persons may be asymptomatic, or present as illness ranging from a mild cough illness to classic pertussis with persistent cough (i.e., lasting more than 7 days). Inspiratory whoop is not common.

Even though the disease may be milder in older persons, those who are infected may transmit the disease to other susceptible persons, including unimmunized or incompletely immunized infants. Older persons are often found to have the first case in a household with multiple pertussis cases, and are often the source of infection for children.

Complications

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

complications. Data from 1997–2000 indicate that pneumonia occurred in 5.2% of all reported pertussis cases, and among 11.8% of infants younger than 6 months of age.



Neurologic complications such as seizures and encephalopathy (a diffuse disorder of the brain) may occur as a result of hypoxia (reduction of oxygen supply) from coughing, or possibly from toxin. Neurologic complications of pertussis are more common among infants. Other less serious complications of pertussis include otitis media, anorexia, and dehydration. Complications resulting from pressure effects of severe paroxysms include pneumothorax, epistaxis, subdural hematomas, hernias, and rectal prolapse.

In 2004–05 a total of 66 deaths from pertussis were reported to the National Immunization Program. Children 3 months of age or younger accounted for 56 (85%) of these deaths.

Adolescents and adults may also develop complications of pertussis, such as difficulty sleeping, urinary incontinence, pneumonia, and rib fracture.

Laboratory Diagnosis

The diagnosis of pertussis is based on a characteristic clinical history (cough for more than 2 weeks with whoop, paroxysms, or posttussive vomiting) as well as a variety of laboratory tests (culture, polymerase chain reaction [PCR], direct fluorescent antibody [DFA] and serology).

Culture is considered the gold standard laboratory test and is the most specific of the laboratory tests for pertussis. However, fastidious growth requirements make *B. pertussis* difficult to culture. The yield of culture can be affected by specimen collection, transportation, and isolation techniques. Specimens from the posterior nasopharynx, not the throat, should be obtained using Dacron® or calcium alginate (not cotton) swabs. Isolation rates are highest during the first 3 to 4 weeks of illness (catarrhal and early paroxysmal stages). Cultures are variably positive (30%–50%) and may take as long as 2 weeks, so results may be too late for clinical usefulness. Cultures are less likely to be positive if performed later in the course of illness (more than 2 weeks after cough onset) or on specimens from persons who have received antibiotics or have been vaccinated. Since adolescents and adults have often been coughing for several weeks before they seek medical attention, it is often too late for culture to be useful.

Because of the increased sensitivity and faster reporting of results of PCR, many laboratories are now using this method exclusively. PCR should be used in addition to, and not as a replacement for culture. No PCR product has been

approved by the Food and Drug Administration (FDA), and there are no standardized protocols, reagents, or reporting formats for pertussis PCR testing. Consequently, PCR assays vary widely among laboratories. Specificity can be poor, with high rates of false-positive results in some laboratories. Like culture, PCR is also affected by specimen collection. An inappropriately obtained nasopharyngeal swab will likely be negative by both culture and PCR. PCR is less affected by prior antibiotic therapy, since the organism does not need to be viable to be positive by PCR. Continued use of culture is essential for confirmation of PCR results.

DFA testing of nasopharyngeal specimens may be useful as a rapid screening test for pertussis. Use of the monoclonal DFA test has improved the specificity, but DFA still has a low sensitivity and should not be relied upon as a criterion for laboratory confirmation.

Serologic testing could be useful for adults and adolescents who present late in the course of their illness, when both culture and PCR are likely to be negative. However, there is no FDA-approved diagnostic test. The currently available serologic tests measure antibodies that could result from either infection or vaccination, so a positive serologic response simply means that the person has been exposed to pertussis by either recent or remote infection or by recent or remote vaccination. Since vaccination can induce both IgM and IgA antibodies (in addition to IgG antibodies), use of such serologic assays cannot differentiate infection from vaccine response. At this time, serologic test results should not be relied upon for case confirmation of pertussis infection.

An elevated white blood cell count with a lymphocytosis is usually present in classical disease of infants. The absolute lymphocyte count often reaches 20,000 or greater. However, there may be no lymphocytosis in some infants and children or in persons with mild or modified cases of pertussis. More information on the laboratory diagnosis of pertussis is available at http://www.cdc.gov/nip/publications/surv-manual/chpt08_pertussis.pdf

Medical Management

The medical management of pertussis cases is primarily supportive, although antibiotics are of some value. Erythromycin is the drug of choice. This therapy eradicates the organism from secretions, thereby decreasing communicability and, if initiated early, may modify the course of the illness.

An antibiotic effective against pertussis (such as azithromycin, erythromycin or trimethoprim-sulfamethoxazole) should be administered to all close contacts of persons with pertussis, regardless of age and vaccination status. Revised treatment and postexposure prophylaxis recommendations

were published in December 2005 (see reference list). All close contacts younger than 7 years of age who have not completed the four-dose primary series should complete the series with the minimal intervals. (see table in Appendix A). Close contacts who are 4–6 years of age and who have not yet received the second booster dose (usually the fifth dose of DTaP) should be vaccinated. The administration of Tdap to persons 10 through 64 years of age who have been exposed to a person with pertussis is not contraindicated, but the efficacy of postexposure use of Tdap is unknown.

Epidemiology

Occurrence

Pertussis occurs worldwide.

Reservoir

Pertussis is a human disease. No animal or insect source or vector is known to exist. Adolescents and adults are an important reservoir for B. pertussis and are often the source of infection for infants.

Transmission

Transmission most commonly occurs by the respiratory route through contact with respiratory droplets, or by contact with airborne droplets of respiratory secretions. Transmission occurs less frequently by contact with freshly contaminated articles of an infected person.

Temporal Pattern

Pertussis has no distinct seasonal pattern, but it may increase in the summer and fall.

Communicability

Pertussis is highly communicable, as evidenced by secondary attack rates of 80% among susceptible household contacts. Persons with pertussis are most infectious during the catarrhal period and the first 2 weeks after cough onset (i.e., approximately 21 days).

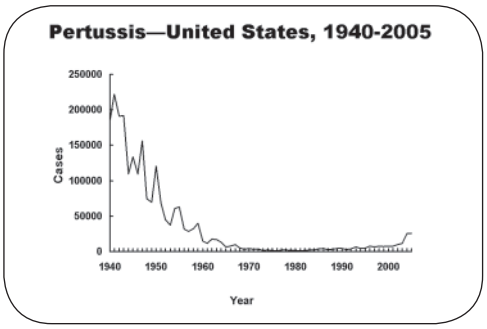
Pertussis Epidemiology

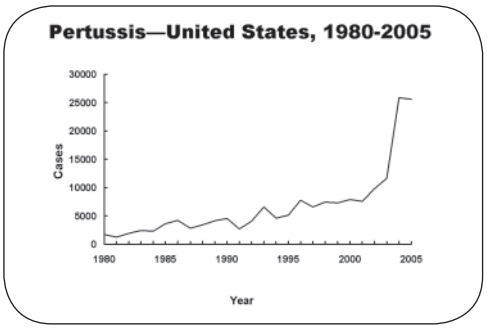
• Reservoir	Human Adolescents and adults
• Transmission	Respiratory droplets
• Communicability	Maximum in catarrhal stage Secondary attack rate up to 80%

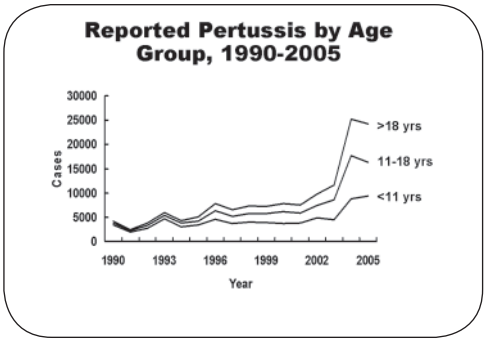
Secular Trends in the United States

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).

Pertussis







Following introduction of whole-cell pertussis vaccine in the 1940s, pertussis incidence gradually declined, reaching 15,000 reported cases in 1960 (approximately 8 per 100,000 population). By 1970, annual incidence was fewer than 5,000 cases per year, and during 1980–1990, an average of 2,900 cases per year were reported (approximately 1 per 100,000 population).

Pertussis incidence has been gradually increasing since the early 1980s. A total of 25,827 cases was reported in 2004, the largest number since 1959. The reasons for the increase are not clear.

During 2001–2003, the highest average annual pertussis incidence was among infants younger than 1 year of age (55.2 cases per 100,000 population), and particularly among children younger than 6 months of age (98.2 per 100,000 population). In 2002, 24% of all reported cases were in this age group. However, in recent years, adolescents (11–18 years of age) and adults (19 years and older) have accounted for an increasing proportion of cases. During 2001–2003, the annual incidence of pertussis among persons aged 10–19 years increased from 5.5 per 100,000 in 2001, to 6.7 in 2002, and 10.9 in 2003. In 2004 and 2005, approximately 60% of reported cases were among persons 11 years of age and older. Increased recognition and diagnosis of pertussis in older age groups probably contributed to this increase of reported cases among adolescents and adults.

Of the 10,650 children 3 months to 4 years of age with reported pertussis during 1990–1996 and known vaccination status, 54% were not age-appropriately vaccinated with DTaP.

Pertussis Surveillance

Pertussis cases are reported to CDC via two systems. States provide information about cases of pertussis, including demographic information, through the National Electronic Transmittal System for Surveillance. More detailed information is reported to CDC through the Supplementary Pertussis Surveillance System. Although many pertussis cases are not reported, the surveillance system is useful for monitoring epidemiologic trends. For instance, although the highest incidence of pertussis occurs in infancy, the age group at greatest risk for severe illness and complications, in recent years, the surveillance system has reflected an increase in the incidence of pertussis in all age groups, most notably among adolescents and adults.

Guidelines on pertussis surveillance and outbreak control are available at http://www.cdc.gov/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.

Pertussis Vaccines

Whole-Cell Pertussis Vaccine

Whole-cell pertussis vaccine is composed of a suspension of formalin-inactivated *B. pertussis* cells. It was developed in the 1930s and used widely in clinical practice by the mid-1940s.

Based on controlled efficacy trials conducted in the 1940s and on subsequent observational efficacy studies, a primary series of four doses of whole-cell DTP vaccine was 70%–90% effective in preventing serious pertussis disease. Protection decreased with time, resulting in little or no protection 5 to 10 years following the last dose. Local reactions such as redness, swelling, and pain at the injection site occurred following up to half of doses of whole-cell DTP vaccines. Fever and other mild systemic events were also common. Concerns about safety led to the development of more purified (acellular) pertussis vaccines that are associated with a lower frequency of adverse reactions. Whole-cell pertussis vaccines are no longer available in the United States but are still used in many other countries.

Whole-Cell Pertussis Vaccine

- Developed in mid-1930s and combined as DTP in mid-1940s
- 70%-90% efficacy after 3 doses
- Protection for 5-10 years
- Local adverse reactions common

Acellular Pertussis 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

Acellular Pertussis Vaccine

Characteristics

Acellular pertussis vaccines are subunit vaccines that contain purified, inactivated components of *B. pertussis* cells. Several acellular pertussis vaccines have been developed for different age groups; these contain different pertussis components in varying concentrations. Acellular pertussis vaccines are available only as combinations with tetanus and diphtheria toxoids.

Pediatric Formulation (DTaP)

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, pertactin, and fimbriae types 2 and 3. None of the available DTaP vaccines contains thimerosal as a preservative, although Infanrix and Daptacel contain 2-phenoxyethanol as a preservative. Tripedia does not contain a preservative. All three vaccines are supplied in single-dose vials or syringes.

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 compared with 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 the same five pertussis components as Daptacel but with a reduced quantity of PT. Adacel contains aluminum phosphate as an adjuvant and does not contain a preservative. Both vaccines are supplied 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.

DTaP Clinical Trials

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

Tdap

Adolescent and adult formulation Tdap vaccines were licensed on the basis of noninferiority of the serologic response to the various components compared with each company's pediatric DTaP formulation (Infanrix and Daptacel) among persons who had received pediatric DTaP or DTP in childhood. For both vaccines, the antibody response to a single dose of Tdap was similar to that following three doses of DTaP in infants. This type of study is known as "bridging." The new vaccines are assumed to have similar clinical efficacy as DTaP vaccine since a similar level of antibody to the components was achieved.

Vaccination Schedule and Use

DTaP

The primary series of DTaP vaccine consists of four doses, the first three doses given at 4- to 8-week intervals (minimum of 4 weeks), beginning at 6 weeks to 2 months of age. The fourth dose is given 6–12 months after the third to maintain adequate immunity for the ensuing preschool years. DTaP should be administered simultaneously with all other indicated vaccines.

Routine DTaP Primary Vaccination Schedule

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

The fourth dose of all brands of DTaP is licensed, and recommended by ACIP, to be administered at 15–18 months of age (17–20 months for Daptacel). However, ACIP

DTaP Fourth Dose

- Recommended at 15-18 months*
- May be given earlier if:
  - child is 12 months of age, and
  - 6 months since DTaP3, and
  - unlikely to return at 15-18 months

*17-20 months for Daptacel

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

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

Tdap Vaccines

- Boostrix (GlaxoSmithKline)
  - —approved for persons 10-18 years of age
- Adacel (sanofi pasteur)
  - —approved for persons 11-64 years of age

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.

Children who received all four primary doses before the fourth birthday should receive a fifth (booster) dose of DTaP before entering school. This booster dose is not necessary (but may be given) if the fourth dose in the primary series was given on or after the fourth birthday. The booster dose increases antibody levels and may decrease the risk of school-age children transmitting the disease to younger siblings who are not fully vaccinated. Infanrix and Tripedia are approved for the fifth dose following a series of four doses of DTaP.

For children who started the vaccination series with whole-cell DTP, DTaP should be substituted for any remaining doses of the pertussis series.

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 do 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.

ACIP recommends that adolescents 11–12 years of age should receive a single dose of Tdap instead of Td.

Adolescents 13–18 years who have not received Tdap should receive a single dose of Tdap as their catch-up booster instead of Td if they have completed the recommended childhood DTaP/DTP vaccination series, and have not yet received a Td booster.

A 5-year interval between Td and Tdap is encouraged to reduce the risk of local and systemic adverse reactions. However, ACIP did not define an absolute minimum interval between Td and Tdap. The interval between Td and Tdap may be shorter than 5 years if protection from pertussis needed. The decision whether to administer Tdap when less than 5 years has elapsed since the last dose of Td should be based on whether the benefit of pertussis immunity outweighs the risk of a local adverse reaction. An interval of less than 5 years can be considered in situations of increased risk of pertussis, such as during a pertussis outbreak, or if protection is needed because of household or other close contact with an infant younger than 12 months of age or a young child who has not been vaccinated against pertussis.

ACIP recommends that adults 19 through 64 years of age receive a single dose of Adacel to replace a single dose of Td for booster immunization against tetanus, diphtheria and pertussis. Adacel may be given at an interval less than 10 years since receipt of the last tetanus toxoid-containing vaccine to protect against pertussis. Special emphasis should be placed on Tdap vaccination of adults who have close contact with infants, such as childcare and healthcare personnel, and parents. Ideally, Tdap should be given at least 1 month before beginning close contact with the infant.

Any woman who might become pregnant is encouraged to receive a single dose of Tdap if she has not already received a dose. Women who have not received Tdap (including women who are breastfeeding) should receive a dose in the immediate postpartum period, before discharge from the hospital or birthing center, if 2 years or more have elapsed since the last Td. Shorter intervals since the last Td can be used if necessary. If Tdap cannot be administered before discharge, it should be given as soon as feasible. The dose of Tdap replaces the next routine dose of Td.

ACIP recommends Td when tetanus and diphtheria protection is required during pregnancy. However, pregnancy is not a contraindication for use of Tdap. A clinician may choose to administer Tdap to a pregnant woman in certain circumstances, such as during a community pertussis outbreak. When Td or Tdap is administered during pregnancy, the second or third trimester is preferred to avoid coincidental association of vaccination and spontaneous termination of

Recommendations for Tdap Vaccination of Adolescents

- Adolescents 11-12 years of age should receive a single dose of Tdap instead of Td*
- Adolescents 13-18 years who have not received Tdap should receive a single dose of Tdap as their catch-up booster instead of Td*

*if the person has completed the recommended childhood DTaP/DTP vaccination series, and has not yet received a Td booster

MMWR 2006;55(RR-3):1-43

Minimum Interval Between Td and Tdap

- A 5-year interval since the last Td dose is encouraged to reduce the chance of a local reaction
- ACIP did not define an absolute minimum interval between Td and Tdap
- Interval between Td and Tdap may be shorter if protection from pertussis needed
- Decision to administer Tdap based on whether the benefit of pertussis immunity outweighs the risk of a local adverse reaction

MMWR 2006;55(RR-3):1-43

Recommendations for Tdap Vaccination of Adults

- Single dose of Adacel to replace a single dose of Td
- May be given at an interval less than 10 years since receipt of last tetanus toxoid-containing vaccine
- Special emphasis on adults with close contact with infants (e.g., childcare and healthcare personnel, and parents)

MMWR 2006;55(RR-17):1-37

Use of Tdap Among Pregnant Women*

- Any woman who might become pregnant is encouraged to receive a single dose of Tdap
- Women who have not received Tdap should receive a dose in the immediate postpartum period
- ACIP recommends Td when tetanus and diphtheria protection is required during pregnancy
- Pregnancy is not a contraindication for Tdap
- Clinician may choose to administer Tdap to a pregnant woman in certain circumstances (such as during a community pertussis outbreak)

*Provisional recommendations approved by ACIP June 28, 2006

Tdap Vaccine and Healthcare Personnel

- Healthcare personnel who work in hospitals or ambulatory care settings and have direct patient contact should receive a single dose of Tdap (Adacel only) as soon as feasible*
- Priority should be given to vaccination of healthcare personnel who have direct contact with infants 12 months of age and younger
- An interval as short as 2 years (or less) from the last dose of Td is recommended for the Tdap dose

*if they have not previously received Tdap
MMWR 2006;55(RR-17):1-37

Tdap For Persons Without A History of DTP or DTaP

- All adolescents and adults should have documentation of having received a series of DTaP, DTP, DT, or Td
- Persons without documentation should receive a series of 3 vaccinations
- Preferred schedule:
  - —single dose of Tdap*
  - —Td at least 4 weeks after the Tdap dose
  - —second dose of Td at least 6 months after the Td dose

*off-label recommendation. *MMWR* 2006;55(RR-3):1-43

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 or older following any Hib vaccine*

*booster dose should follow prior dose by at least 2 months

a pregnancy, which is more common in the first trimester. Clinicians can choose to administer Tdap instead of Td to pregnant adolescents for routine or "catch-up" vaccination because the incidence of pertussis is high among adolescents. Others for whom Tdap might be considered during pregnancy are pregnant healthcare personnel and child care providers (to prevent transmission to infants younger than 12 months of age and to other vulnerable persons) and pregnant women employed in an institution or living in a community with increased pertussis activity.

Healthcare personnel who work in hospitals or ambulatory care settings and have direct patient contact should receive a single dose of Tdap (Adacel only) as soon as feasible. Priority should be given to vaccination of healthcare personnel who have direct contact with infants 12 months of age and younger. An interval as short as 2 years (or less) from the last dose of Td is recommended for the Tdap dose.

Tdap vaccine may be given at the same visit, or any time before or after any other vaccine.

Immunity following pertussis is not permanent. Persons with a history of pertussis should receive a single dose of Tdap if it is otherwise indicated.

All adolescents and adults should have documentation of having received a primary series of at least three doses of tetanus and diphtheria toxoids during their lifetime. A person without such documentation should receive a series of three doses of tetanus- and diphtheria-containing vaccine. One of these doses, preferably the first, should be Tdap if the person is at least 10 years of age (the minimum age approved for one of the two available Tdap products). The remaining two doses should be adult formulation Td.

No pertussis vaccine is approved for children 7–9 years of age or for persons older than 64 years. ACIP does not recommend the use of Tdap in persons in these age groups.

Combination Vaccines Containing DTaP

TriHIBit

One combination DTaP-Hib (*Haemophilus influenzae* type b) vaccine is currently available in the United States (TriHIBit, 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). TriHIBit can be used if the child is 12 months of age or older, has received at least one prior dose of Hib vaccine 2 or more months earlier, and TriHIBit will be the last dose in the Hib series. For example, TriHIBit can be used for the booster dose at 12–15 months of age in a child who has received Comvax or PedvaxHib at 2 and 4 months of age, or three prior doses of HibTiter or ActHib. TriHIBit can also be used at 15–59 months of age in a child who has received at least one prior dose of any Hib-containing vaccine. TriHIBit should not be used if the child has received no prior Hib doses.

Pediarix

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

The minimum age for the first dose of Pediarix is 6 weeks, so it cannot be used for the birth dose of the hepatitis B series. Pediarix is approved for the first three doses of the DTaP and inactivated polio vaccine (IPV) series, which are usually given at about 2, 4, and 6 months of age; it is not approved for fourth or fifth (booster) doses of the DTaP or IPV series. However, Pediarix is approved for use through

Pediarix

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

6 years of age. A child who is behind schedule can receive Pediarix as long as it is given for doses 1, 2, or 3 of the series, and the child is younger than 7 years of age.

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

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

Pediarix

- May be used interchangeably with other pertussis-containing vaccines if necessary
- Can be given at 2, 4, and 6 months to infants who received a birth dose of hepatitis B vaccine (total of 4 doses)
- May be used in infants whose mothers are HBsAg positive or status is not known*

*off-label recommendation

Other DTaP Issues

In certain circumstances, vaccination with DTaP vaccine should be delayed until a child with a known or suspected neurologic condition has been evaluated, treatment initiated, and the condition stabilized. These conditions include the presence of an evolving neurologic disorder (e.g., uncontrolled epilepsy, infantile spasms, and progressive encephalopathy), a history of seizures that has not been evaluated, or a neurologic event that occurs between doses of pertussis vaccine.

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

A family history of seizures or other neurologic diseases, or stable or resolved neurologic conditions (e.g., controlled idiopathic epilepsy, cerebral palsy, developmental delay) are not contraindications to pertussis vaccination. Acetaminophen or ibuprofen may be administered to children with such histories or conditions at the time of DTaP vaccination and for 24 hours thereafter to reduce the possibility of postvaccination fever, which could cause a febrile seizure.

Reducing the dose of whole-cell DTP or DTaP vaccine or giving the full dose in multiple smaller doses may result in an altered immune response and inadequate protection. Furthermore, there is no evidence that the chance of a significant vaccine reaction is likely to be reduced by this practice. The use of multiple reduced doses that together equal a full immunizing dose, or the use of smaller, divided doses is not endorsed or recommended. Any vaccination using less than the standard dose should not be counted, and the person should be revaccinated according to age.

Pertussis Vaccination of Children Who Have Recovered From Pertussis

- If documented disease, do not need additional doses of pediatric pertussis vaccine*
- Satisfactory documentation of disease:
  - —recovery of *B. pertussis* on culture, or
  - —typical symptoms and clinical course when epidemiologically linked to a culture-confirmed case

*Tdap is recommended when the child is age eligible

Children who have recovered from documented pertussis do not need additional doses of pediatric pertussis vaccine. However, Tdap vaccine is recommended when the child

becomes age eligible. Satisfactory documentation includes recovery of *B. pertussis* on culture or typical symptoms and clinical course when these are epidemiologically linked to a culture-confirmed case, as may occur during outbreaks. When such confirmation of diagnosis is lacking, vaccination should be completed because cough illness may be caused by other *Bordetella* species, other bacteria, or certain viruses.

Adverse Reactions Following Vaccination

DTaP

As with all injected vaccines, administration of DTaP may cause local reactions, such as pain, redness, or swelling. Local reactions have been reported in 20%–40% of children after the first three doses. Local reactions appear to be more frequent after the fourth and/or fifth doses. Mild systemic reactions such as drowsiness, fretfulness, and low-grade fever may also occur. Temperature of 101°F or higher is reported in 3%–5% of DTaP recipients. These reactions are self-limited and can be managed with symptomatic treatment with acetaminophen or ibuprofen. Moderate or severe systemic reactions (such as fever [105°F or higher], febrile seizures, persistent crying lasting 3 hours or longer, and hypotonic hyporesponsive episodes) have been reported after administration of DTaP but occur less frequently than among children who received whole-cell DTP. Rates of these less common reactions vary by symptom and vaccine but generally occur in fewer than 1 in 10,000 doses. See the pertussis chapter in the textbook *Vaccines* (Plotkin and Orenstein, eds., 2003) for a comprehensive review of DTaP adverse event data.

DTaP Adverse Reactions

- Local reactions (pain, redness, swelling) 20%-40%
- Temp of 101°F or higher 3%-5%
- More severe adverse reactions not common
- Local reactions more common following 4th and 5th doses

Information on adverse reactions following a full series of DTaP is also limited. Available data suggest a substantial increase in the frequency and magnitude of local reactions after the fourth and fifth doses. For example, swelling at the site of injection occurred in 2% of patients after the first dose of Tripedia, and in 29% following the fourth dose. Increases in the frequency of fever after the fourth dose have also been reported, although the increased frequencies of other systemic reactions (e.g., fretfulness, drowsiness, or decreased appetite) have not been observed. Further details on this issue can be found in a supplemental ACIP statement published in 2000 (*MMWR* 2000;49(No RR-13):1–8).

Adverse Reactions Following the 4th and 5th DTaP Dose

- Local adverse reactions and fever increased with 4th and 5th doses of DTaP
- Reports of swelling of entire limb
- Extensive swelling after 4th dose NOT a contraindication to 5th dose

Swelling involving the entire thigh or upper arm has been reported after booster doses of certain acellular pertussis vaccines. The limb swelling may be accompanied by erythema, pain and fever. Although the swelling may interfere with walking, most children have no limitation of activity. The pathogenesis and frequency of substantial local reactions and limb swelling are not known, but these conditions appear to be self-limited and resolve without sequelae.

ACIP recommends that a fifth dose of DTaP be administered before a child enters school. It is not known whether children who experience entire limb swelling after a fourth dose of DTaP are at increased risk for this reaction after the fifth dose. Because of the importance of this dose in protecting a child during school years, ACIP recommends that a history of extensive swelling after the fourth dose should not be considered a contraindication to receipt of a fifth dose at school entry. Parents should be informed of the increase in reactogenicity that has been reported following the fourth and fifth doses of DTaP.

Tdap Adverse Reactions

- Local reactions (pain, redness, swelling) 21%-66%
- Temp of 100.4°F or higher 1.4%
- Adverse reactions occur at approximately the same rate as Td alone (without acellular pertussis vaccine)

Tdap

The safety of Tdap vaccines was evaluated as part of prelicensure studies. The most common adverse reaction following both brands of Tdap vaccine is a local reaction, such as pain (66%), redness (25%) or swelling (21%) at the site of injection. Temperature of 100.4°F or higher was reported by 1.4% of Tdap recipients and 1.1% of Td recipients. Tdap recipients also reported a variety of nonspecific systemic events, such as headache, fatigue and gastrointestinal symptoms. Local reactions, fever, and nonspecific systemic symptoms occurred at approximately the same rate in recipients of Tdap and the comparison group that received Td without acellular pertussis vaccine. No serious adverse events have been attributed to Tdap.

Contraindications and Precautions to Vaccination

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

Contraindications to further vaccination with DTaP are a 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.

DTaP Precautions*

- Moderate or severe acute illness
- Temperature 105°F (40.5°C) or higher within 48 hours with no other identifiable cause
- Collapse or shock-like state (hypotonic hyporesponsive episode) within 48 hours
- Persistent, inconsolable crying lasting 3 hours or longer, occurring within 48 hours
- Convulsions with or without fever occurring within 3 days

*may consider use in outbreaks

Moderate or severe acute illness is a precaution to vaccination. Children with mild illness, such as otitis media or upper respiratory infection, should be vaccinated. Children for whom vaccination is deferred because of moderate or severe acute illness should be vaccinated when their condition improves.

Certain infrequent adverse reactions following DTaP vaccination are considered to be precautions for subsequent doses of pertussis vaccine. These adverse reactions are a temperature of 105°F (40.5°C) or higher within 48 hours that is not due

to another identifiable cause; collapse or shock-like state (hypotonic hyporesponsive episode) within 48 hours; persistent, inconsolable crying lasting 3 hours or longer, occurring within 48 hours; and convulsions with or without fever occurring within 3 days.

There are circumstances (e.g., during a communitywide outbreak of pertussis) in which the benefit of vaccination outweighs the risk, even if one of the four precautionary adverse reactions occurred following a prior dose. In these circumstances, one or more additional doses of pertussis vaccine should be considered. DTaP should be used in these circumstances.

Tdap

Tdap is contraindicated for persons with a history of a severe allergic reaction to a vaccine component or following a prior dose of vaccine. Tdap is also contraindicated for persons with a history of encephalopathy not due to another identifiable cause occurring within 7 days after administration of a pertussis-containing vaccine.

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

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.

Tdap Precautions

- History of Guillain-Barré syndrome within 6 weeks after a previous dose of tetanus toxoid-containing vaccine
- Progressive neurologic 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

As noted above, certain conditions following DTaP vaccine, such as temperature of 105°F or higher, collapse or shock-like state, persistent crying, or convulsions with or without fever are a precaution to subsequent doses of DTaP. However, occurrence of one of these adverse reactions following DTaP vaccine in childhood is not a contraindication or precaution to administration of Tdap to an adolescent or adult. A history of extensive limb swelling following DTaP is not a contra-indication to Tdap vaccination. A stable neurologic disorder (such as controlled seizures or cerebral palsy), pregnancy, breastfeeding, and immunosuppression are not contraindications or precautions to administration of Tdap.

Pertussis-Containing Vaccines Storage and Handling

- Stored at 35°–46°F (2°–8°C) at all times
- Must never be frozen
- Vaccine exposed to freezing temperature must not be administered and should be discarded
- Should not be used after the expiration date printed on the box or label

Vaccine Storage and Handling

DTaP, Td and Tdap vaccines should be stored at 35°–46°F (2°–8°C) at all times. The vaccines must never be frozen. Vaccine exposed to freezing temperature must not be administered and should be discarded. DTaP, Td and Tdap should not be used after the expiration date printed on the box or label.

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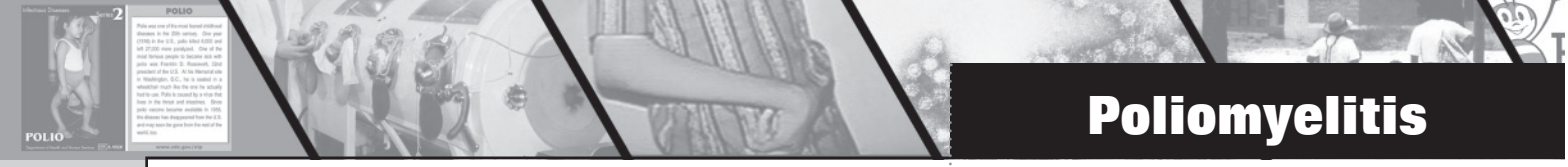
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Pertussis

7



Poliomyelitis

The words polio (grey) and myelon (marrow, indicating the spinal cord) are derived from the Greek. It is the effect of poliomyelitis virus on the spinal cord that leads to the classic manifestation of paralysis.

Records from antiquity mention crippling diseases compatible with poliomyelitis. Michael Underwood first described a debility of the lower extremities in children that was recognizable as poliomyelitis in England in 1789. The first outbreaks in Europe were reported in the early 19th century, and outbreaks were first reported in the United States in 1843. For the next hundred years, epidemics of polio were reported from developed countries in the Northern Hemisphere each summer and fall. These epidemics became increasingly severe, and the average age of persons affected rose. The increasingly older age of persons with primary infection increased both the disease severity and number of deaths from polio. Polio reached a peak in the United States in 1952, with more than 21,000 paralytic cases. However, following introduction of effective vaccines, polio incidence declined rapidly. The last case of wild-virus polio acquired in the United States was in 1979, and global polio eradication may be achieved within the next decade.

Poliomyelitis

- First described by Michael Underwood in 1789
- First outbreak described in U.S. in 1843
- More than 21,000 paralytic cases reported in the U.S. in 1952
- Global eradication within next decade

Poliovirus

Poliovirus is a member of the enterovirus subgroup, family Picornaviridae. Enteroviruses are transient inhabitants of the gastrointestinal tract, and are stable at acid pH. Picornaviruses are small, ether-insensitive viruses with an RNA genome.

There are three poliovirus serotypes (P1, P2, and P3). There is minimal heterotypic immunity between the three serotypes. That is, immunity to one serotype does not produce significant immunity to the other serotypes.

The poliovirus is rapidly inactivated by heat, formaldehyde, chlorine, and ultraviolet light.

Poliovirus

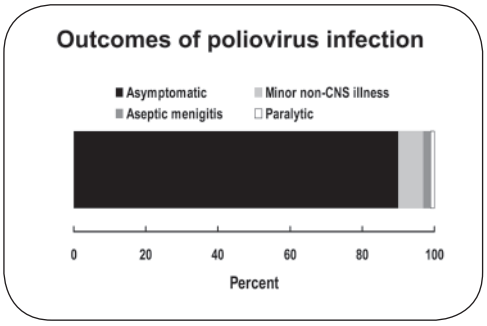
- Enterovirus (RNA)
- Three serotypes: 1, 2, 3
- Minimal heterotypic immunity between serotypes
- Rapidly inactivated by heat, formaldehyde, chlorine, ultraviolet light

Pathogenesis

The virus enters through the mouth, and primary multiplication of the virus occurs at the site of implantation in the pharynx and gastrointestinal tract. The virus is usually present in the throat and in the stool before the onset of illness. One week after onset there is less virus in the throat, but virus continues to be excreted in the stool for several weeks. The virus invades local lymphoid tissue, enters the bloodstream, and then may infect cells of the central nervous system. Replication of poliovirus in motor neurons of the anterior horn and brain stem results in cell destruction and causes the typical manifestations of poliomyelitis.

Poliomyelitis Pathogenesis

- Entry into mouth
- Replication in pharynx, GI tract, local lymphatics
- Hematologic spread to lymphatics and central nervous system
- Viral spread along nerve fibers
- Destruction of motor neurons



Clinical Features

The incubation period for poliomyelitis is commonly 6 to 20 days with a range of 3 to 35 days.

The response to poliovirus infection is highly variable and has been categorized on the basis of the severity of clinical presentation.

Up to 95% of all polio infections are inapparent or asymptomatic. Estimates of the ratio of inapparent to paralytic illness vary from 50:1 to 1,000:1 (usually 200:1). Infected persons without symptoms shed virus in the stool and are able to transmit the virus to others.

Approximately 4%–8% of polio infections consist of a minor, nonspecific illness without clinical or laboratory evidence of central nervous system invasion. This clinical presentation is known as abortive poliomyelitis, and is characterized by complete recovery in less than a week. Three syndromes observed with this form of poliovirus infection are upper respiratory tract infection (sore throat and fever), gastrointestinal disturbances (nausea, vomiting, abdominal pain, constipation or, rarely, diarrhea), and influenza-like illness. These syndromes are indistinguishable from other viral illnesses.

Nonparalytic aseptic meningitis (symptoms of stiffness of the neck, back, and/or legs), usually following several days after a prodrome similar to that of minor illness, occurs in 1%–2% of polio infections. Increased or abnormal sensations can also occur. Typically these symptoms will last from 2 to 10 days, followed by complete recovery.

Fewer than 1% of all polio infections result in flaccid paralysis. Paralytic symptoms generally begin 1 to 10 days after prodromal symptoms and progress for 2 to 3 days. Generally, no further paralysis occurs after the temperature returns to normal. The prodrome may be biphasic, especially in children, with initial minor symptoms separated by a 1- to 7-day period from more major symptoms. Additional prodromal signs and symptoms can include a loss of superficial reflexes, initially increased deep tendon reflexes and severe muscle aches and spasms in the limbs or back. The illness progresses to flaccid paralysis with diminished deep tendon reflexes, reaches a plateau without change for days to weeks, and is usually asymmetrical. Strength then begins to return. Patients do not experience sensory losses or changes in cognition.

Many persons with paralytic poliomyelitis recover completely and, in most, muscle function returns to some degree. Weakness or paralysis still present 12 months after onset is usually permanent.

Paralytic polio is classified into three types, depending on the level of involvement. Spinal polio is most common, and during 1969–1979, accounted for 79% of paralytic cases. It is characterized by asymmetric paralysis that most often involves the legs. Bulbar polio leads to weakness of muscles innervated by cranial nerves and accounted for 2% of cases during this period. Bulbospinal polio, a combination of bulbar and spinal paralysis, accounted for 19% of cases.

The death-to-case ratio for paralytic polio is generally 2%–5% among children and up to 15%–30% for adults (depending on age). It increases to 25%–75% with bulbar involvement.

Laboratory Diagnosis

Viral Isolation

Poliovirus may be recovered from the stool or pharynx of a person with poliomyelitis. Isolation of virus from the cerebrospinal fluid (CSF) is diagnostic, but is rarely accomplished.

If poliovirus is isolated from a person with acute flaccid paralysis, it must be tested further, using oligonucleotide mapping (fingerprinting) or genomic sequencing, to determine if the virus is "wild type" (that is, the virus that causes polio disease) or vaccine type (virus that could derive from a vaccine strain).

Serology

Neutralizing antibodies appear early and may be at high levels by the time the patient is hospitalized; therefore, a fourfold rise in antibody titer may not be demonstrated.

Cerebrospinal Fluid

In poliovirus infection, the CSF usually contains an increased number of white blood cells (10–200 cells/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 2005, only 1,948 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 to 10 days before onset Virus present in stool 3 to 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.)

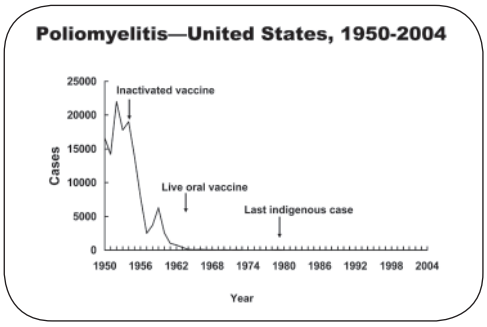
In the immediate prevaccine era, improved sanitation allowed less frequent exposure and increased the age of primary infection. Boosting of immunity from natural exposure became more infrequent and the number of susceptible persons accumulated, ultimately resulting in the occurrence of epidemics, with 13,000 to 20,000 paralytic cases reported annually.

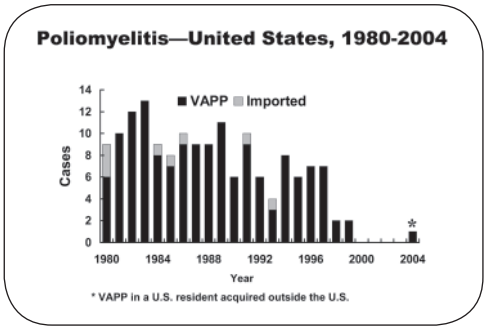
In the early vaccine era, the incidence dramatically decreased after the introduction of inactivated polio vaccine (IPV) in 1955. The decline continued following oral polio vaccine (OPV) introduction in 1961. In 1960, a total of 2,525 paralytic cases were reported, compared with 61 in 1965.

The last cases of paralytic poliomyelitis caused by endemic transmission of wild virus in the United States were in 1979, when an outbreak occurred among the Amish in several

Midwest states. The virus was imported from the Netherlands. From 1980 through 1999, a total of 152 confirmed cases of paralytic poliomyelitis were reported, an average of 8 cases per year. Six cases were acquired outside the United States and imported. The last imported case was reported in 1993. Two cases were classified as indeterminant (no poliovirus isolated from samples obtained from the patients, and patients had no history of recent vaccination or direct contact with a vaccine recipient). The remaining 144 (95%) cases were vaccine-associated paralytic polio (VAPP) caused by live oral polio vaccine.

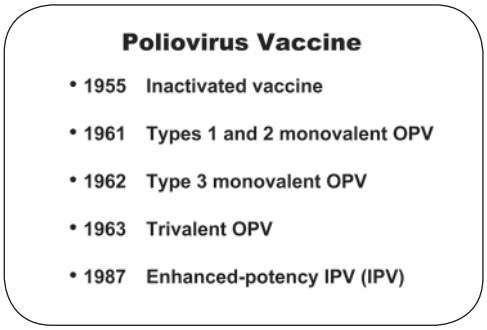
In order to eliminate VAPP from the United States, ACIP recommended in 2000 that IPV be used exclusively in the United States. The last case of VAPP acquired in the United States was reported in 1999. In 2005, an unvaccinated U.S. resident was infected with polio vaccine virus in Costa Rica and subsequently developed VAPP. Also in 2005, several asymptomatic infections with a vaccine-derived poliovirus were detected in unvaccinated children in Minnesota. The source of the vaccine virus has not been determined, but it appeared to have been circulating among humans for at least 2 years based on genetic changes in the virus. No VAPP has been reported from this virus.





Poliovirus Vaccines

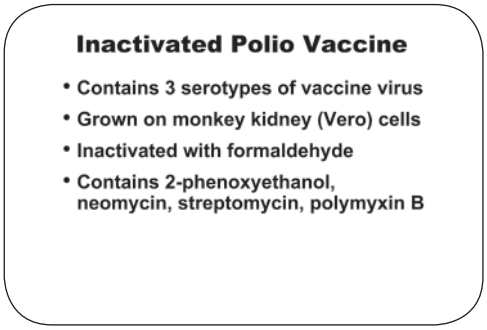
Inactivated poliovirus vaccine (IPV) was licensed in 1955 and was used extensively from that time until the early 1960s. In 1961, type 1 and 2 monovalent oral poliovirus vaccine (MOPV) was licensed, and in 1962, type 3 MOPV was licensed. In 1963, trivalent OPV was licensed and largely replaced IPV use. Trivalent OPV was the vaccine of choice in the United States and most other countries of the world after its introduction in 1963. An enhanced-potency IPV was licensed in November 1987 and first became available in 1988. Use of OPV was discontinued in the United States in 2000.



Characteristics

Inactivated poliovirus vaccine

Two enhanced forms of inactivated poliovirus vaccine are currently licensed in the United States, but only one vaccine (IPOL, sanofi pasteur) is actually distributed. This vaccine contains all three serotypes of polio vaccine virus. The viruses are grown in a type of monkey kidney tissue culture (Vero cell line) and inactivated with formaldehyde. The vaccine contains 2-phenoxyethanol as a preservative, and trace amounts of neomycin, streptomycin, and polymyxin B. It is supplied in a single-dose prefilled syringe and should be administered by either subcutaneous or intramuscular injection.



Oral 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% or more immune after 2 doses
- At least 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
- Approximately 50% immune after 1 dose
- More than 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 weeks
6-18 months	IPV	4 weeks
4-6 years*	IPV	4 weeks

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

The first and second doses of IPV are necessary to induce a primary immune response, and the third dose of IPV ensures "boosting" of antibody titers to high levels. The preferred interval between the second and third doses of IPV is 2–8 months. However, if accelerated protection is needed, the minimum interval between all doses of IPV is 4 weeks, and the minimum age for the fourth dose is 18 weeks. Children who receive three doses of IPV before the fourth birthday should receive a fourth dose before or at school entry. The fourth dose is not needed if the third dose is given on or after the fourth birthday. If all four IPV doses are administered after 6 weeks of age and are all separated by at least 4 weeks, a fifth dose is not needed, even if the fourth dose was administered before 4 years of age (except if a specific state school entry requirement mandates a dose of polio vaccine on or after the fourth birthday). It is not necessary to repeat or add doses if the interval between doses is prolonged.

Schedules that Include Both IPV and OPV

- Only IPV is available in the United States
- Schedule begun with OPV should be completed with IPV
- Any combination of 4 doses of IPV and OPV by 4-6 years of age constitutes a complete series

Only IPV is available for routine polio vaccination of children in the United States. A polio vaccination schedule begun with OPV should be completed with IPV. If a child receives both types of vaccine, four doses of any combination of IPV or OPV by 4–6 years of age is considered a complete poliovirus vaccination series. A minimum interval of 4 weeks should separate all doses of the series.

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 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.

Polio Vaccination of Adults

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

Some adults, however, are at increased risk of infection with poliovirus. These include travelers to areas where poliomyelitis is endemic or epidemic (currently limited to South Asia, the eastern Mediterranean, and Africa), laboratory workers handling specimens that may contain polioviruses, and healthcare personnel in close contact with patients who may be excreting wild polioviruses. In addition, members of specific population groups with a current disease caused by wild polioviruses (e.g., during an outbreak) are also at increased risk.

Recommendations for poliovirus vaccination of adults in the above categories depend upon the previous vaccination history and the time available before protection is required.

- For unvaccinated adults (including adults without a written record of prior polio vaccination) at increased risk of exposure to poliomyelitis, primary immunization with IPV is recommended. The recommended schedule is two doses separated by 1–2 months, and a third dose given 6–12 months after the second dose.

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

In some circumstances time will not allow completion of this schedule. If 8 weeks or more are available before protection is needed, three doses of IPV should be given at least 4 weeks apart. If 4 to 8 weeks are available before protection is needed, two doses of IPV should be given at least 4 weeks apart. If less than 4 weeks are available before protection is needed, a single dose of IPV is recommended. In all instances, the remaining doses of vaccine should be given later, at the recommended intervals, if the person remains at increased risk.

- 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).

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

- 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 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 and older
- Increased risk in persons with immunodeficiency
- No procedure available for identifying persons at risk of paralytic disease
- 5-10 cases per year with exclusive use of OPV
- Most cases in healthy children and their household contacts

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 immunocompetent. Compared with immunocompetent children, the risk of VAPP is almost 7,000 times higher for persons with certain types of immunodeficiencies, particularly B-lymphocyte disorders (e.g., agammaglobulinemia and hypogammaglobulinemia), which reduce the synthesis of immune globulins. There is no procedure available for identifying persons at risk of paralytic disease, except excluding older persons and screening for immunodeficiency.

From 1980 through 1998, 152 cases of paralytic polio were reported in the United States; 144 (95%) of these cases were VAPP, and the remaining eight were in persons who acquired documented or presumed wild-virus polio outside the United States. Of the 144 VAPP cases, 59 (41%) occurred in healthy vaccine recipients (average age 3 months). Forty-four (31%) occurred in healthy contacts of vaccine recipients (average age 26 years), and 7 (5%) were community acquired (i.e., vaccine virus was recovered but there was no known contact with a vaccine recipient). Thirty-four (24%) of VAPP cases occurred in persons with immunologic abnormalities (27 in vaccine recipients and 7 in contacts of vaccine recipients). None of the vaccine recipients were known to be immunologically abnormal prior to vaccination.

The risk of VAPP is not equal for all OPV doses in the vaccination series. The risk of VAPP is 7 to 21 times higher for the first dose than for any other dose in the OPV series. From 1980 through 1994, 303 million doses of OPV were

distributed and 125 cases of VAPP were reported, for an overall risk of VAPP of one case per 2.4 million doses. Forty-nine paralytic cases were reported among immunocompetent recipients of OPV during this period. The overall risk to these recipients was one VAPP case per 6.2 million OPV doses. However, 40 (82%) of these 49 cases occurred following receipt of the first dose, making the risk of VAPP one case per 1.4 million first doses. The risk for all other doses was one per 27.2 million doses. The reason for this difference by dose is not known with certainty, but it is probably because the vaccine virus is able to replicate longer in a completely nonimmune infant. This prolonged replication increases the chance of the emergence of a revertant virus that may cause paralysis. The situation is similar for contacts. A nonimmune child may shed virus longer, increasing the chance of exposure of a contact.

The last case of VAPP acquired in the United States was reported in 1999. As noted 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

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* type b**

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

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 influenzae* type b**
Pathogenesis

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

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 prevaccine era. Hallmarks of Hib meningitis are fever, decreased mental status, and stiff neck (these symptoms also occur with meningitis caused by other bacteria). Hearing impairment or other neurologic sequelae occur in 15%–30% of survivors. The case-fatality rate is 2%–5%, despite appropriate antimicrobial therapy.

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

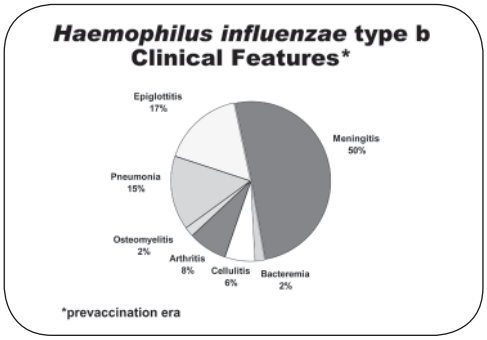
Septic arthritis (joint infection), cellulitis (rapidly progressing skin infection which usually involves face, head, or neck), and pneumonia (which can be mild focal or severe empyema) are common manifestations of invasive disease.

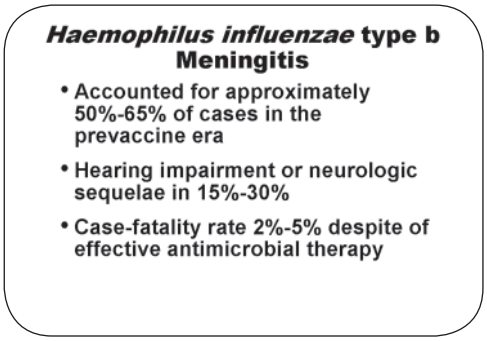
Osteomyelitis (bone infection) and pericarditis (infection of the sac covering the heart) are less common forms of invasive disease. Otitis media and acute bronchitis due to *H. influenzae* are generally caused by nontypeable strains. Hib strains account for only 5%–10% of *H. influenzae* causing otitis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

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

Laboratory Diagnosis

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





All isolates of *H. influenzae* should be serotyped. This is an extremely important laboratory procedure that should be performed on every isolate of *H. influenzae*, especially those obtained from children younger 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.

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**
Medical Management

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

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.

***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

Temporal Pattern

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

Communicability

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

Secular Trends in the United States

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

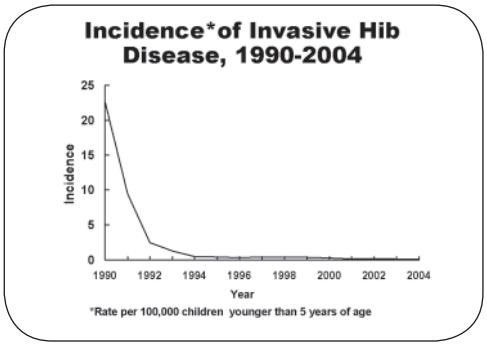
Before the availability of national reporting data, several areas conducted active surveillance for *H. influenzae* disease, which allowed estimates of disease nationwide. In the early 1980s, it was estimated that about 20,000 cases occurred annually in the United States, primarily among children younger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

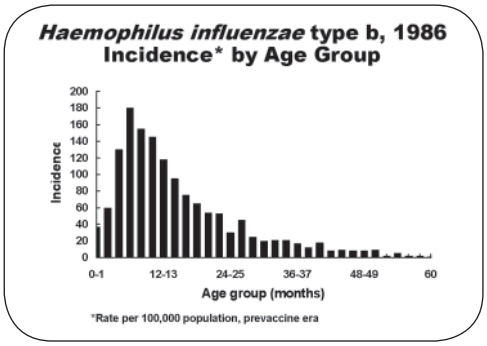
From 1996 through 2000, an average of 1,247 invasive *H. influenzae* infections per year were reported to CDC in all age groups (range 1,162–1,398 per year). Of these, an average of 272 (approximately 22%) per year were among children younger than 5 years of age. Serotype was known for 76% of the invasive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

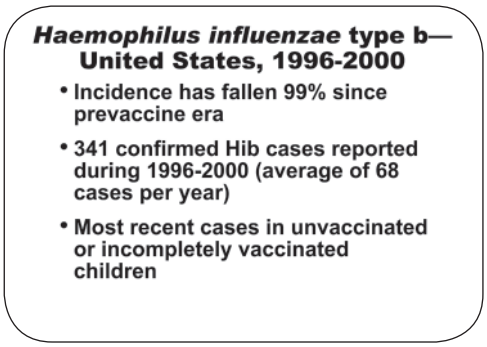
There is evidence that Hib vaccines decrease the rate of carriage of Hib among vaccinated children, thereby decreasing the chance that unvaccinated children will be exposed.

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

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







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

In 2005, among children younger than 5 years of age, 9 cases of invasive disease due to Hib were reported in the United States. In addition, another 217 cases caused by unknown *H. influenzae* serotypes were reported, so the actual number of Hib cases could be between 9 and 226. Most cases were among unvaccinated or incompletely vaccinated children.

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

***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 younger than 18 months of age
- Effectiveness in older children variable

Polysaccharide Vaccines

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

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 younger than 6 weeks of age may induce immunologic tolerance to Hib antigen
- Minimum age 6 weeks

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

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

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.

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.

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

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

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.

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

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

Vaccination of Older Children and Adults

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

Combination Vaccines Containing Hib

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

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 or older following any Hib vaccine series*
- Should not be used if child has receive no prior Hib doses

*booster dose should follow prior dose by at least 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 at 6 weeks of age or older
- 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 Event Reporting System (VAERS) (http://vaers.hhs.gov/).

Contraindications and Precautions to Vaccination

***Haemophilus influenzae* type b Vaccine Contraindications and Precautions**

- Severe allergic reaction to vaccine component or following a prior dose
- Moderate or severe acute illness
- Age younger than 6 weeks

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

Contraindications and precautions for the use of TriHIBit 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 personnel should report any case of invasive Hib disease to local and state health departments.

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Haemophilus influenzae type b

9



Measles

Measles is an acute viral infectious disease. References to measles can be found from as early as the 7th century. The disease was described by the Persian physician Rhazes in the 10th century as "more dreaded than smallpox."

In 1846, Peter Panum described the incubation period of measles and lifelong immunity after recovery from the disease. Enders and Peebles isolated the virus in human and monkey kidney tissue culture in 1954. The first live attenuated vaccine was licensed for use in the United States in 1963 (Edmonston B strain).

Before a vaccine was available, infection with measles virus was nearly universal during childhood, and more than 90% of persons were immune by age 15 years. Measles is still a common and often fatal disease in developing countries. The World Health Organization estimates there were more than 30 million cases and 454,000 deaths from measles in 2004.

Measles

- Highly contagious viral illness
- First described in 7th century
- Near universal infection of childhood in prevaccination era
- Common and often fatal in developing countries

Measles Virus

The measles virus is a paramyxovirus, genus *Morbillivirus*. It is 100–200 nm in diameter, with a core of single-stranded RNA, and is closely related to the rinderpest and canine distemper viruses. Two membrane envelope proteins are important in pathogenesis. They are the F (fusion) protein, which is responsible for fusion of virus and host cell membranes, viral penetration, and hemolysis, and the H (hemagglutinin) protein, which is responsible for adsorption of virus to cells.

There is only one antigenic type of measles virus. Although studies have documented changes in the H glycoprotein, these changes do not appear to be epidemiologically important (i.e., no change in vaccine efficacy has been observed).

Measles virus is rapidly inactivated by heat, light, acidic pH, ether, and trypsin. It has a short survival time (less than 2 hours) in the air or on objects and surfaces.

Measles Virus

- Paramyxovirus (RNA)
- Hemagglutinin important surface antigen
- One antigenic type
- Rapidly inactivated by heat and light

Pathogenesis

Measles is a systemic infection. The primary site of infection is the respiratory epithelium of the nasopharynx. Two to three days after invasion and replication in the respiratory epithelium and regional lymph nodes, a primary viremia occurs with subsequent infection of the reticuloendothelial system. Following further viral replication in regional and distal reticuloendothelial sites, a second viremia occurs 5–7 days after initial infection. During this viremia, there may be infection of the respiratory tract and other organs. Measles virus is shed from the nasopharynx beginning with the prodrome until 3–4 days after rash onset.

Measles Pathogenesis

- Respiratory transmission of virus
- Replication in nasopharynx and regional lymph nodes
- Primary viremia 2-3 days after exposure
- Secondary viremia 5-7 days after exposure with spread to tissues

Measles

Measles Clinical Features

- Incubation period 10-12 days

Prodrome

- Stepwise increase in fever to 103°F or higher
- Cough, coryza, conjunctivitis
- Koplik spots

Measles Clinical Features

Rash

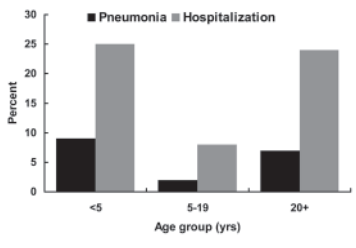
- 2-4 days after prodrome, 14 days after exposure
- Persists 5-6 days
- Begins on face and head
- Maculopapular, becomes confluent
- Fades in order of appearance

Measles Complications

Condition	Percent reported
Diarrhea	8
Otitis media	7
Pneumonia	6
Encephalitis	0.1
Seizures	0.6 – 0.7
Death	0.2

Based on 1985-1992 surveillance data

Measles Complications by Age Group



Clinical Features

The incubation period of measles, from exposure to prodrome averages 10–12 days. From exposure to rash onset averages 14 days (range, 7–18 days).

The prodrome lasts 2–4 days (range 1–7 days). It is characterized by fever, which increases in stepwise fashion, often peaking as high as 103°–105°F. This is followed by the onset of cough, coryza (runny nose), or conjunctivitis.

Koplik spots, a rash (enanthem) present on mucous membranes, is considered to be pathognomonic for measles. It occurs 1–2 days before the rash to 1–2 days after the rash, and appears as punctate blue-white spots on the bright red background of the buccal mucosa.

The measles rash is a maculopapular eruption that usually lasts 5–6 days. It begins at the hairline, then involves the face and upper neck. During the next 3 days, the rash gradually proceeds downward and outward, reaching the hands and feet. The maculopapular lesions are generally discrete, but may become confluent, particularly on the upper body. Initially, lesions blanch with fingertip pressure. By 3–4 days, most do not blanch with pressure. Fine desquamation occurs over more severely involved areas. The rash fades in the same order that it appears, from head to extremities.

Other symptoms of measles include anorexia, diarrhea, especially in infants, and generalized lymphadenopathy.

Complications

Approximately 30% of reported measles cases have one or more complications. Complications of measles are more common among children younger than 5 years of age and adults 20 years of age and older.

From 1985 through 1992, diarrhea was reported in 8% of measles cases, making this the most commonly reported complication of measles. Otitis media was reported in 7% of cases and occurs almost exclusively in children. Pneumonia (in 6% of reported cases) may be viral or superimposed bacterial, and is the most common cause of death.

Acute encephalitis occurs in approximately 0.1% of reported cases. Onset generally occurs 6 days after rash onset (range 1–15 days) and is characterized by fever, headache, vomiting, stiff neck, meningeal irritation, drowsiness, convulsions, and coma. Cerebrospinal fluid shows pleocytosis and elevated protein. The case-fatality rate is approximately 15%. Some form of residual neurologic damage occurs in as many as 25% of cases. Seizures (with or without fever) are reported in 0.6%–0.7% of cases.

Death from measles was reported in approximately 0.2% of the cases in the United States from 1985 through 1992. As with other complications of measles, the risk of death is higher among young children and adults. Pneumonia accounts for about 60% of deaths. The most common causes of death are pneumonia in children and acute encephalitis in adults.

Subacute sclerosing panencephalitis (SSPE) is a rare degenerative central nervous system disease believed to be due to persistent measles virus infection of the brain. Onset occurs an average of 7 years after measles (range 1 month–27 years), and occurs in five to ten cases per million reported measles cases. The onset is insidious, with progressive deterioration of behavior and intellect, followed by ataxia (awkwardness), myoclonic seizures, and eventually death. SSPE has been extremely rare since the early 1980s.

Measles illness during pregnancy results in a higher risk of premature labor, spontaneous abortion, and low-birthweight infants. Birth defects (with no definable pattern of malformation) have been reported rarely, without confirmation that measles was the cause.

Atypical measles occurs only in persons who received inactivated ("killed") measles vaccine (KMV) and are subsequently exposed to wild-type measles virus. An estimated 600,000 to 900,000 persons received KMV in the United States from 1963 to 1967. KMV sensitizes the recipient to measles virus antigens without providing protection. Subsequent infection with measles virus leads to signs of hypersensitivity polyserositis. The illness is characterized by fever, pneumonia, pleural effusions, and edema. The rash is usually maculopapular or petechial, but may have urticarial, purpuric, or vesicular components. It appears first on the wrists or ankles. Atypical measles may be prevented by revaccinating with live measles vaccine. Moderate to severe local reactions with or without fever may follow vaccination; these reactions are less severe than with infection with wild measles virus.

Modified measles occurs primarily in patients who received immune globulin (IG) as postexposure prophylaxis and in young infants who have some residual maternal antibody. It is usually characterized by a prolonged incubation period, mild prodrome, and sparse, discrete rash of short duration. Similar mild illness has been reported among previously vaccinated persons.

Rarely reported in the United States, hemorrhagic measles is characterized by high fever (105°–106°F), seizures, delirium, respiratory distress, and hemorrhage into the skin and mucous membranes.

Measles in an immunocompromised person may be severe with a prolonged course. It is reported almost exclusively in persons with T-cell deficiencies (certain leukemias, lymphomas, and acquired immunodeficiency syndrome [AIDS]). It may occur without the typical rash, and a patient may shed virus for several weeks after the acute illness.

Measles in developing countries has resulted in high attack rates among children younger than 12 months of age. Measles is more severe in malnourished children, particularly those with vitamin A deficiency. Complications include diarrhea, dehydration, stomatitis, inability to feed, and bacterial infections (skin and elsewhere). The case-fatality rate may be as high as 25%. Measles is also a leading cause of blindness in African children.

Measles Laboratory Diagnosis

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

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

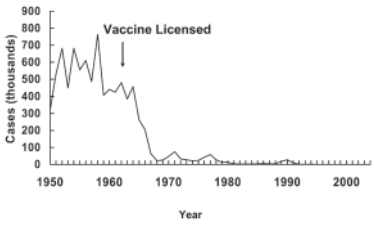
Measles transmission is primarily person to person via large respiratory droplets. Airborne transmission via aerosolized droplet nuclei has been documented in closed areas (e.g., office examination room) for up to 2 hours after a person with measles occupied the area.

Measles Epidemiology

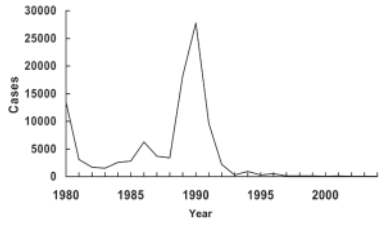
• Reservoir	Human
• Transmission	Respiratory Airborne
• Temporal pattern	Peak in late winter–spring
• Communicability	4 days before to 4 days after rash onset

Measles

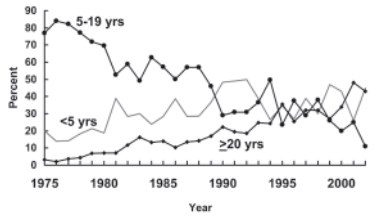
Measles—United States, 1950-2004



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 or longer, and
- Temperature 101°F (38.3°C) or higher, and
- Cough or coryza or conjunctivitis

Epidemiologic Classification

An international imported case has its source outside the country, rash onset occurs within 21 days after entering the country, and illness cannot be linked to local transmission.

An indigenous case is any case that cannot be proved to be imported. Subclasses of indigenous cases exist; for more information, see CDC Manual for Surveillance of Vaccine-Preventable Diseases (available on the 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, non-communicable 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.

Measles (MMR) Vaccine Indications

- All children 12 months of age and older
- Susceptible adolescents and adults without documented evidence of immunity

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.

Measles-Mumps-Rubella Vaccine

- 12 months is the recommended and minimum age
- MMR given before 12 months should not be counted as a valid dose
- Revaccinate at 12 months of age or older

A second dose of MMR is recommended to produce immunity in those who failed to respond to the first dose. The second dose of MMR vaccine should routinely be given at age 4–6 years, before a child enters kindergarten or first grade. The recommended visit at age 11–12 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.

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

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

Second Dose of Measles Vaccine

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

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 wor*ker has administered the vaccine or has seen a record that documents vaccination. Persons who lack adequate documentation of vaccination or other acceptable evidence of immunity should be vaccinated. Vaccination status and receipt of all vaccinations should be documented in the patient's permanent medical record and in a vaccination record held by the individual.

MMRV is approved by the Food and Drug Administration for children 12 months through 12 years of age (that is, until the 13th birthday). 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.

Vaccination of Adults

Adults at Increased Risk of Measles

- College students
- International travelers
- Healthcare personnel

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, mumps, 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, mumps, 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, mumps, and rubella immunity, medical facilities should consider recommending a dose of MMR vaccine to 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.

Measles Immunity in Healthcare Personnel

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

Serologic screening need not be done before vaccinating for measles and rubella unless the medical facility considers it cost-effective. Serologic testing is appropriate only if tracking systems are used to ensure that tested persons who are identified as susceptible are subsequently vaccinated in a timely manner. Serologic testing for immunity to measles and rubella is not necessary for persons documented to be appropriately vaccinated or who have other acceptable evidence of immunity. If the return and timely vaccination of those screened cannot be assured, serologic testing before vaccination should not be done.

Persons who travel outside the United States are at increased risk of exposure to measles. Measles is endemic or epidemic in many countries throughout the world. Although proof of immunization is not required for entry into the United States or any other country, persons traveling or living abroad should have evidence of measles immunity. Adequate vaccination of persons who travel outside the United States is two doses of MMR.

Revaccination

Revaccination is recommended for certain persons. The following groups should be considered unvaccinated and should receive at least one dose of measles vaccine: persons 1) vaccinated before the first birthday, 2) vaccinated with killed measles vaccine (KMV), 3) vaccinated with KMV followed by live vaccine less than 4 months after the last 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.)

Measles Vaccine Indications for Revaccination

- Vaccinated before the first birthday
- Vaccinated with killed measles vaccine
- Vaccinated prior to 1968 with an unknown type of vaccine
- Vaccinated with IG in addition to a further attenuated strain or vaccine of unknown type

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 30,000–40,000 vaccinated susceptible persons, with a temporal clustering of cases occurring 2–3 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 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 immuno-suppression
- 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. 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.

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 skin testing (TST) is not a prerequisite for vaccination with MMR or other measles-containing vaccine. TST has no effect on the response to MMR vaccination. However, measles vaccine (and possibly mumps, rubella, and varicella vaccines) may transiently suppress the response to TST in a person infected with *Mycobacterium tuberculosis*. If tuberculin skin testing is needed at the same time as administration of measles-containing vaccine, TST and vaccine can be administered at the same visit. Simultaneously administering TST and measles-containing vaccine does not interfere with reading the TST result at 48–72 hours and ensures that the person has received measles vaccine. If the measles-containing vaccine has been administered recently, TST screening should be delayed at least 4 weeks after vaccination. A delay in administering TST will remove the concern of any theoretical suppression of TST reactivity from the vaccine. TST screening can be performed and read before administering the measles-containing vaccine. This option is the least favored because it will delay receipt of the vaccine.

Tuberculin Skin Testing (TST)* and Measles Vaccine

- Apply TST at same visit as MMR
- Delay TST at least 4 weeks if MMR given first
- Apply TST first and administer MMR when skin test read (least favored option because receipt of MMR is delayed)

*previously called PPD

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. A multistate mumps outbreak in 2006 resulted in more than 6,000 reported cases.

Mumps

- Acute viral illness
- Parotitis and orchitis described by Hippocrates in 5th century BCE
- Viral etiology described by Johnson and Goodpasture in 1934
- Frequent cause of outbreaks among military personnel in prevaccine era

Mumps Virus

Mumps virus is a paramyxovirus in the same group as parainfluenza and Newcastle disease virus. Parainfluenza and Newcastle disease viruses produce antibodies that cross-react with mumps virus. The virus has a single-stranded RNA genome.

The virus can be isolated or propagated in cultures of various human and monkey tissues and in embryonated eggs. It has been recovered from the saliva, cerebrospinal fluid, urine, blood, milk, and infected tissues of patients with mumps.

Mumps virus is rapidly inactivated by formalin, ether, chloroform, heat, and ultraviolet light.

Mumps Virus

- Paramyxovirus
- RNA virus
- One antigenic type
- Rapidly inactivated by chemical agents, heat, and ultraviolet light

Pathogenesis

The virus is acquired by respiratory droplets. It replicates in the nasopharynx and regional lymph nodes. After 12–25 days a viremia occurs, which lasts from 3–5 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

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 (inflammatory cells in cerebrospinal fluid) is common, occurring asymptomatically is common, occuring asymptomatically 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).

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)

Orchitis (testicular inflammation) is the most common complication in postpubertal males. It occurs in as many as 50% of postpubertal males, usually after parotitis, but it may precede it, begin simultaneously, or occur alone. It is bilateral in approximately 30% of affected males. There is usually abrupt onset of testicular swelling, tenderness, nausea, vomiting, and fever. Pain and swelling may subside in 1 week, but tenderness may last for weeks. Approximately 50% of patients with orchitis have some degree of testicular atrophy, but sterility is rare.

Oophoritis (ovarian inflammation) occurs in 5% of postpubertal females. It may mimic appendicitis. There is no relationship to impaired fertility.

Pancreatitis is infrequent, but occasionally occurs without parotitis; the hyperglycemia is transient and is reversible. Although single instances of diabetes mellitus have been reported, a causal relationship with mumps virus infection has yet to be conclusively demonstrated; many cases of temporal association have been described both in siblings and individuals, and outbreaks of diabetes have been reported a few months or years after outbreaks of mumps.

Deafness caused by mumps virus occurs in approximately 1 per 20,000 reported cases. Hearing loss is unilateral in approximately 80% of cases and may be associated with vestibular reactions. Onset is usually sudden and results in permanent hearing impairment.

Electrocardiogram changes compatible with myocarditis are seen in 3%–15% of patients with mumps, but symptomatic involvement is rare. Complete recovery is the rule, but deaths have been reported.

Other less common complications of mumps include arthralgia, arthritis, and nephritis. An average of one death from mumps per year was reported during 1980–1999.

Laboratory Diagnosis

The diagnosis of mumps is usually suspected based on clinical manifestations, in particular the presence of parotitis.

Mumps virus can be isolated from clinical specimens. The preferred sample for viral isolation is a swab from the parotid duct, or the duct of another affected salivary gland. Collection of viral samples from persons suspected of having mumps is strongly recommended. Mumps virus can also be detected by polymerase chain reaction (PCR).

Serology is the simplest method for confirming mumps virus infection and enzyme immunoassay (EIA), is the most commonly used test. EIA is widely available and is more sensitive than other serologic tests. It is available for both IgM and IgG. IgM antibodies usually become detectable during the first few days of illness and reach a peak about a week after onset. However, as with measles and rubella, mumps IgM may be transient or missing in persons who have had any doses of mumps-containing vaccine. Sera should be collected as soon as possible after symptom onset for IgM testing or as the acute-phase specimen for IgG seroconversion. Convalescent-phase sera should be collected 2 weeks later. A negative serologic test, especially in a vaccinated person, should not be used to rule out a mumps diagnosis because the tests are not sensitive enough to detect infection in all persons with clinical illness. In the absence of another diagnosis, a person meeting the clinical case definition should be reported as a mumps case.

Mumps Laboratory Diagnosis

- Isolation of mumps virus
- Detection of mumps antigen by PCR
- Serologic testing
  - —positive IgM antibody
  - —significant increase in IgG antibody between acute and convalescent specimens

Epidemiology

Occurrence

Mumps occurs worldwide.

Reservoir

Mumps is a human disease. Although persons with asymptomatic or nonclassical infection can transmit the virus, no carrier state is known to exist.

Transmission

Mumps is spread through airborne transmission or by direct contact with infected droplet nuclei or saliva.

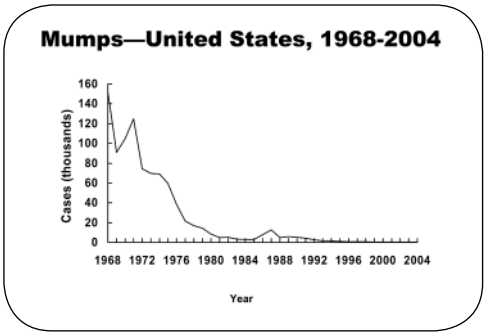
Temporal Pattern

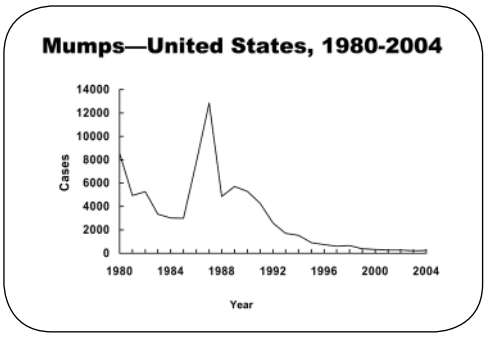
Mumps incidence peaks predominantly in late winter and spring, but the disease has been reported throughout the year.

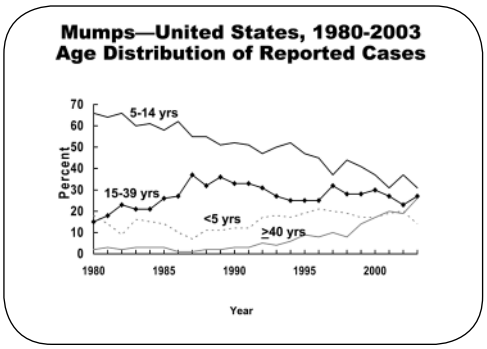
Mumps Epidemiology

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

Mumps







Communicability

Contagiousness is similar to that of influenza and rubella, but is less than that for measles or varicella. The infectious period is considered to be from 3 days before to the 4th day of active disease; virus has been isolated from saliva 7 days before to 9 days after onset of parotitis.

Secular Trends in the United States

Mumps became a nationally reportable disease in the United States in 1968. However, an estimated 212,000 cases occurred in the United States in 1964. Following vaccine licensure, reported mumps decreased rapidly. Approximately 3,000 cases were reported annually in 1983–1985 (1.3–1.55 cases per 100,000 population).

In 1986 and 1987, there was a relative resurgence of mumps, which peaked in 1987, when 12,848 cases were reported. The highest incidence of mumps during the resurgence was among older school-age and college-age youth (10–19 years of age), who were born before routine mumps vaccination was recommended. Mumps incidence in this period correlated with the absence of comprehensive state requirements for mumps immunization. Several mumps outbreaks among highly vaccinated school populations were reported, indicating that high coverage with a single dose of mumps vaccine did not always prevent disease transmission, probably because of vaccine failure.

Since 1989, the number of reported mumps cases has steadily declined, from 5,712 cases to a total of 258 cases in 2004. In 2006 a multistate mumps outbreak resulted in more than 6,000 reported cases. Eight states in the Midwest reported the majority of cases. The outbreak peaked in mid-April. The median age of persons reported with mumps was 22 years. Many cases occurred among college students, many of whom had received one or two doses of MMR vaccine.

Before vaccine licensure in 1967, and during the early years of vaccine use, most reported cases occurred in the 5–9-year age group; 90% of cases occurred among children 15 years of age and younger. In the late 1980s, there was a shift towards older children. Since 1990, persons age 15 years and older have accounted for 30%–40% of cases per year (42% in 2002). Males and females are affected equally.
Eighty percent or more of adults in urban and suburban areas with or without a history of mumps have serologic evidence of immunity.

Case Definition

The clinical case definition of mumps is an acute onset of unilateral or bilateral tender, self-limited swelling of the parotid or other salivary gland lasting more than 2 days and without other apparent cause.

Mumps Clinical Case Definition

- Acute onset of unilateral or bilateral tender, self-limited swelling of the parotid or other salivary gland lasting more than 2 days and without other apparent cause

Mumps Vaccine

Characteristics

Mumps virus was isolated in 1945, and an inactivated vaccine was developed in 1948. This vaccine produced only short-lasting immunity, and its use was discontinued in the mid-1970s. The currently used Jeryl Lynn strain of live attenuated mumps virus vaccine was licensed in December 1967.

Mumps vaccine is available 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	At least 1 dose

- Should be administered with measles and rubella (MMR) or with measles, rubella and varicella (MMRV)

Immunogenicity and Vaccine Efficacy

Mumps vaccine produces an inapparent, or mild, noncommunicable infection. More than 97% of recipients of a single dose develop measurable antibody. Seroconversion rates are similar for single antigen mumps vaccine, MMR, and MMRV. Postlicensure studies conducted in the United States during 1973–1989 determined that 1 dose of mumps or MMR vaccine was 75%–91% effective. A study from the United Kingdom documented vaccine effectiveness of 88% with 2 doses. The duration of vaccine-induced immunity is believed to be greater than 25 years, and is probably lifelong in most vaccine recipients.

Mumps

Mumps (MMR) Vaccine Indications

- One dose (as MMR) for preschool-age children 12 months of age and older and persons born during or after 1957 not at high risk of mumps exposure
- Second dose (as MMR) for school-age children and adults at high risk of mumps exposure (i.e., healthcare personnel, international travelers and students at post-high school educational institutions

Vaccination Schedule and Use

One dose of mumps-containing vaccine is routinely recommended for all preschool-age children 12 months of age and older and for persons born during or after 1957 not at high risk of mumps exposure. The first dose of mumps-containing vaccine should be given on or after the first birthday. Mumps-containing vaccine given before 12 months of age should not be counted as part of the series. Children vaccinated with mumps-containing vaccine before 12 months of age should be revaccinated with two doses of MMR vaccine, the first of which should be administered when the child is at least 12 months of age.

In 2006, ACIP recommended a second dose of mumps vaccine for school-age children and for adults at high risk of mumps exposure (i.e., healthcare personnel, international travelers, and students at post-high school educational institutions).The combined MMR vaccine is recommended for both doses to ensure immunity to all three viruses.

The second dose of MMR vaccine should be given routinely at age 4–6 years, before a child enters kindergarten or first grade. The recommended 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.

Only doses of vaccine with written documentation of the date of receipt should be accepted as valid. Self-reported doses or a parental report of vaccination is not considered adequate documentation. A clinician should not provide an immunization record for a patient unless that clinician has administered the vaccine or has seen a record that documents vaccination. Persons who lack adequate documentation of vaccination or other acceptable evidence of immunity should be vaccinated. Vaccination status and receipt of all vaccinations should be documented in the patient's permanent medical record and in a vaccination record held by the individual.

MMRV is approved by the Food and Drug Administration for children 12 months through 12 years of age (that is, until the 13th birthday). 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

Although persons born before 1957 can generally be considered to be immune to mumps, ACIP recommends that healthcare facilities should strongly consider recommending 2 doses of MMR vaccine to unvaccinated healthcare workers born before 1957 who do not have other evidence of mumps immunity, such as laboratory evidence of immunity.

Mumps Immunity

- Healthcare facilities should strongly consider recommending 2 doses of MMR vaccine to unvaccinated workers born before 1957 who do not have other evidence of mumps immunity

Postexposure Prophylaxis

Neither mumps immune globulin nor immune globulin (IG) is effective postexposure prophylaxis. Vaccination after exposure is not harmful and may possibly avert later disease.

Adverse Reactions Following Vaccination

Mumps vaccine is very safe. Most adverse events reported following MMR vaccine (such as fever, rash, and joint symptoms) are attributable to the measles or rubella components. No adverse reactions were reported in large-scale field trials. Subsequently, parotitis and fever have been reported rarely. A few cases of orchitis (all suspect) also have been reported.

MMR Adverse Reactions

• Fever	5%-15%
• Rash	5%
• Joint symptoms	25%
• Thrombocytopenia	<1/30,000 doses
• Parotitis	rare
• Deafness	rare
• Encephalopathy	<1/1,000,000 doses

Rare cases of CNS dysfunction, including cases of deafness, within 2 months of mumps vaccination have been reported. The calculated incidence of CNS reactions is approximately one per 800,000 doses of Jeryl Lynn strain of mumps vaccine virus. The Institute of Medicine (1993) concluded that evidence is inadequate to accept or reject a causal relationship between the Jeryl Lynn strain of mumps vaccine and aseptic meningitis, encephalitis, sensorineural deafness, or orchitis.

Allergic reactions, including rash, pruritus, and purpura, have been temporally associated with vaccination, but these are transient and generally mild.

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

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, 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 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 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 virus was first isolated in 1962 by Parkman and Weller. The first rubella vaccines were licensed in 1969.

Rubella
- From Latin meaning "little red"
- Discovered in 18th century - thought to be variant of measles
- First described as distinct clinical entity in German literature
- Congenital rubella syndrome (CRS) described by Gregg in 1941

Rubella Virus

Rubella virus is classified as a togavirus, genus *Rubivirus*. It is most closely related to group A arboviruses, such as eastern and western equine encephalitis viruses. It is an enveloped RNA virus, with a single antigenic type that does not cross-react with other members of the togavirus group. Rubella virus is relatively unstable and is inactivated by lipid solvents, trypsin, formalin, ultraviolet light, low pH, heat, and amantadine.

Rubella Virus
- Togavirus
- RNA virus
- One antigenic type
- Rapidly inactivated by chemical agents, ultraviolet light, low pH, and heat

Pathogenesis

Following respiratory transmission of rubella virus, replication of the virus is thought to occur in the nasopharynx and regional lymph nodes. A viremia occurs 5–7 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 often more prominent after a hot shower or bath. Lymphadenopathy may begin a week before the rash and last several weeks. Postauricular, posterior cervical, and suboccipital nodes are commonly involved.

Arthralgia and arthritis occur so frequently in adults that they are considered by many to be an integral part of the illness rather than a complication. Other symptoms of rubella include conjunctivitis, testalgia, or orchitis. Forschheimer spots may be noted on the soft palate but are not diagnostic for rubella.

Complications

Complications of rubella are not common, but they tend to occur more often in adults than in children.

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

Arthralgia or arthritis may occur in up to 70% of adult women who contract rubella, but it is rare in children and adult males. Fingers, wrists, and knees are often affected. Joint symptoms tend to occur about the same time or shortly after appearance of the rash and may last for up to 1 month; chronic arthritis is rare.

Encephalitis occurs in one in 6,000 cases, more frequently in adults (especially in females) than in children. Mortality estimates vary from 0 to 50%.

Hemorrhagic manifestations occur in approximately one per 3,000 cases, occurring more often in children than in adults. These manifestations may be secondary to low platelets and vascular damage, with thrombocytopenic purpura being the most common manifestation. Gastrointestinal, cerebral, or intrarenal hemorrhage may occur. Effects may last from days to months, and most patients recover.

Additional complications include orchitis, neuritis, and a rare late syndrome of progressive panencephalitis.

Congenital Rubella Syndrome

Prevention of CRS is the main objective of rubella vaccination programs in the United States.

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

A rubella epidemic in the United States in 1964–1965 resulted in 12.5 million cases of rubella infection and about 20,000 newborns with CRS. The estimated cost of the epidemic was $840 million. This does not include the emotional toll on the families involved. 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. Children with CRS have a higher than expected incidence of autism.

Infants with CRS may have low titers by hemagglutination inhibition (HI) but may have high titers of neutralizing antibody that may persist for years. Reinfection may occur. Impaired cell-mediated immunity has been demonstrated in some children with CRS.

Laboratory Diagnosis

Many rash illnesses can mimic rubella infection, and as many as 50% of rubella infections may be subclinical. The only reliable evidence of acute rubella infection is a positive viral culture for rubella or detection of rubella virus by polymerase chain reaction, the presence of rubella-specific IgM antibody, or demonstration of a significant rise in IgG antibody from paired acute- and convalescent-phase sera.

Rubella Laboratory Diagnosis

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

Rubella virus can be isolated from nasal, blood, throat, urine and cerebrospinal fluid specimens from rubella and CRS patients. Virus may be isolated from the pharynx 1 week before and until 2 weeks after rash onset. Although isolation of the virus is diagnostic of rubella infection, viral cultures are labor intensive, and therefore not done in many laboratories; they are generally not used for routine diagnosis of rubella. Viral isolation is an extremely valuable epidemiologic tool and should be attempted for all suspected cases of rubella or CRS. 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.

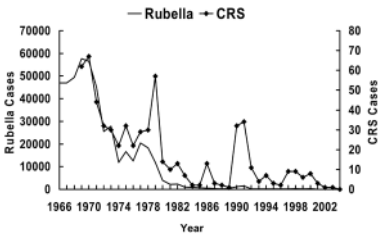
Communicability
Rubella is only moderately contagious. The disease is most contagious when the rash first appears, but virus may be shed from 7 days before to 5–7 days or more after rash onset. Infants with CRS shed large quantities of virus from body secretions for up to 1 year and can therefore transmit rubella to persons caring for them who are susceptible to the disease.

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

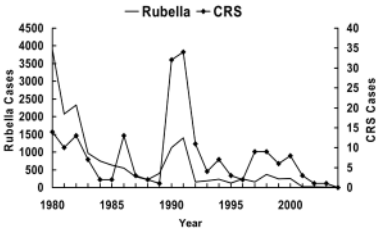
Secular Trends in the United States
Rubella and congenital rubella syndrome became nationally notifiable diseases in 1966. The largest annual total of cases of rubella in the United States was in 1969, when 57,686 cases were reported (58 cases per 100,000 population). Following vaccine licensure in 1969,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

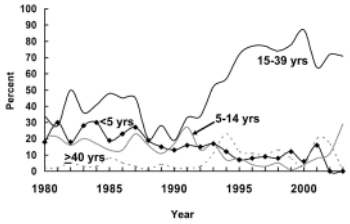


Rubella

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 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	At least 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 and older
- Susceptible adolescents and adults without documented evidence of rubella immunity
- Emphasis on nonpregnant women of childbearing age, particularly those born outside the U.S.

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 12 months of age or older. All persons born during or after 1957 should have documentation of at least one dose of MMR. The first dose of MMR should be given on or after the first birthday. Any dose of rubella-containing vaccine given before 12 months of age should not be counted as part of the series. Children vaccinated with rubella-containing vaccine before 12 months of age should be revaccinated when the child is at least 12 months of age.

A second dose of MMR is recommended to produce immunity to measles and mumps in those who failed to respond to the first dose. Data indicate that almost all persons who do not respond to the measles component of the first dose will respond to a second dose of MMR. Few data on the immune response to the rubella and mumps components of a second dose of MMR are available. However, most persons who do not respond to the rubella or mumps component of the first MMR dose would be expected to respond to the second dose. The second dose is not generally considered a booster dose because a primary immune response to the first dose provides long-term protection. Although a second dose of vaccine may increase antibody titers in some persons who responded to the first dose, available data indicate that these increased antibody titers are not sustained. The combined MMR vaccine is recommended for both doses to ensure immunity to all three viruses.

The second dose of MMR vaccine should routinely be given at age 4–6 years, before a child enters kindergarten or first grade. The recommended 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. The minimum interval between doses of MMRV is 3 months.

All older children not previously immunized should receive at least one dose of rubella vaccine as MMR or MMRV if 12 years of age or younger.

Adults born in 1957 or later who do not have a medical contraindication should receive at least one dose of MMR vaccine unless they have documentation of vaccination with at least one dose of measles-, rubella-, and mumps-containing vaccine or other acceptable evidence of immunity to these three diseases. Some adults at high risk of measles and mumps exposure may require a second dose. This second dose should be administered as combined MMR vaccine (see Measles chapter for details). Efforts should be made to identify and vaccinate susceptible adolescents and adults,

particularly women of childbearing age who are not pregnant. Particular emphasis should be placed on vaccinating both males and females in colleges, places of employment, and healthcare settings.

Only doses of vaccine with written documentation of the date of receipt should be accepted as valid. Self-reported doses or a parental report of vaccination is not considered adequate documentation. A healthcare 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.

MMRV is approved by the Food and Drug Administration for children 12 months through 12 years of age (that is, until the 13th birthday). ACIP has 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.

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)**

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

- **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 at least one 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 vaccine is very safe. Most adverse reactions reported following MMR vaccination (such as fever and rash) are attributable to the measles component. The most common complaints following rubella vaccination are fever, lymphadenopathy, and arthralgia. These adverse reactions only occur in susceptible persons and are more common in adults, especially in women.
Joint symptoms, such as arthralgia (joint pain) and arthri-

MMR Adverse Reactions

• Fever	5%-15%
• Rash	5%
• Joint symptoms	25%
• Thrombocytopenia	<1/30,000 doses
• Parotitis	rare
• Deafness	rare
• Encephalopathy	<1/1,000,000 doses

Rubella Vaccine Arthropathy

- Acute arthralgia in about 25% of vaccinated, susceptible adult women
- Acute arthritis-like signs and symptoms occurs in about 10% of recipients
- Rare reports of chronic or persistent symptoms
- Population-based studies have not confirmed an association with rubella vaccine

tis (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. ACIP does not recommend routine pregnancy screening of

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

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.

Vaccination in Pregnancy Study 1971-1989

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

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 recon-

stituted 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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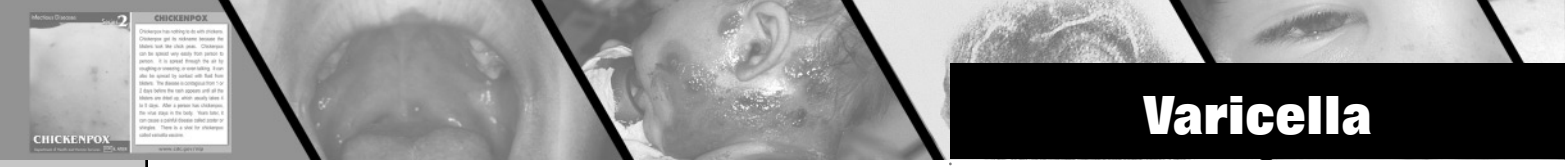
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Varicella

Varicella is an acute infectious disease caused by varicella zoster virus (VZV). The recurrent infection (herpes zoster, also known as shingles) has been recognized since ancient times. Primary varicella infection (chickenpox) was not reliably distinguished from smallpox until the end of the 19th century. In 1875, Steiner demonstrated that chickenpox was caused by an infectious agent by inoculating volunteers with the vesicular fluid from a patient with acute varicella. Clinical observations of the relationship between varicella and herpes zoster were made in 1888 by von Bokay, when children without evidence of varicella immunity acquired varicella after contact with herpes zoster. VZV was isolated from vesicular fluid of both chickenpox and zoster lesions in cell culture by Thomas Weller in 1954. Subsequent laboratory studies of the virus led to the development of a live attenuated varicella vaccine in Japan in the 1970s. The vaccine was licensed for use in the United States in March 1995. The first vaccine to reduce the risk of herpes zoster was licensed in May 2006.

Varicella Zoster Virus

VZV is a DNA virus and is a member of the herpesvirus group. Like other herpesviruses, VZV has the capacity to persist in the body after the primary (first) infection as a latent infection. VZV persists in sensory nerve ganglia. Primary infection with VZV results in chickenpox. Herpes zoster (shingles) is the result of recurrent infection. The virus is believed to have a short survival time in the environment.

Pathogenesis

VZV enters through the respiratory tract and conjunctiva. The virus is believed to replicate at the site of entry in the nasopharynx and in regional lymph nodes. A primary viremia occurs 4–6 days after infection and disseminates the virus to other organs, such as the liver, spleen, and sensory ganglia. Further replication occurs in the viscera, followed by a secondary viremia, with viral infection of the skin. Virus can be cultured from mononuclear cells of an infected person from 5 days before to 1 or 2 days after the appearance of the rash.

Clinical Features

The incubation period is 14–16 days after exposure, with a range of 10–21 days. The incubation period may be prolonged in immunocompromised patients and those who have received postexposure treatment with a varicella antibody–containing product.

Varicella Zoster Virus

- Herpesvirus (DNA)
- Primary infection results in varicella (chickenpox)
- Recurrent infection results in herpes zoster (shingles)
- Short survival in environment

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

Varicella Clinical Features

- Incubation period 14-16 days (range 10-21 days)
- Mild prodrome for 1-2 days
- Rash generally appears first on head; most concentrated on trunk
- Successive crops over several days with lesions present in several stages of development

Varicella

Primary Infection (Chickenpox)

A mild prodrome may precede the onset of a rash. Adults may have 1 to 2 days of fever and malaise prior to rash onset, but in children the rash is often the first sign of disease.

The rash is generalized and pruritic and progresses rapidly from macules to papules to vesicular lesions before crusting. The rash usually appears first on the head, then on the trunk, and then the extremities; the highest concentration of lesions is on the trunk (centripetal distribution). Lesions also can occur on mucous membranes of the oropharynx, respiratory tract, vagina, conjunctiva, and the cornea. Lesions are usually 1–4 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 temperature 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 also may have severe, prolonged illness.

Recovery from primary varicella infection usually results in lifetime immunity. In otherwise healthy persons, a second occurrence of chickenpox is not common, but it can happen, particularly in immunocompromised persons. As with other viral diseases, reexposure to natural (wild) varicella may lead to reinfection that boosts antibody titers without causing clinical illness or detectable viremia.

Recurrent Disease (Herpes Zoster)

Herpes zoster, 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.

Herpes Zoster (Shingles)

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

The vesicular eruption of zoster generally occurs unilaterally in the distribution of a sensory nerve. Most often, this involves the trunk or the fifth cranial nerve. Two to four days prior to the eruption, there may be pain and paresthesia in the involved area. There are few systemic symptoms.

Complications

Varicella

Acute varicella is generally mild and self-limited, but it may be associated with complications. Secondary bacterial infections of skin lesions with *Staphylococcus* or *Streptococcus* are the most common cause of hospitalization and outpatient medical visits. Secondary infection with invasive group A streptococci may cause serious illness and lead to hospitalization or death. Pneumonia following varicella is usually viral but may be bacterial. Secondary bacterial pneumonia is more common in children younger than 1 year of age. Central nervous system manifestations of varicella range from aseptic meningitis to encephalitis. Involvement of the cerebellum, with resulting cerebellar ataxia, is the most common and generally has a good outcome. Encephalitis is an infrequent complication of varicella (estimated 1.8 per 10,000 cases) and may lead to seizures and coma. Diffuse cerebral involvement is more common in adults than in children. Reye syndrome is an unusual complication of varicella and influenza and occurs almost exclusively in children who take aspirin during the acute illness. The etiology of Reye syndrome is unknown. There has been a dramatic decrease in the incidence of Reye syndrome during the past decade, presumably related to decreased use of aspirin by children.

Varicella Complications

- Bacterial infection of skin lesions
- Pneumonia (viral or bacterial)
- Central nervous system manifestations
- Reye syndrome
- Hospitalization: 2-3 per 1,000 cases
- Death: 1 per 60,000 cases
- Postherpetic neuraligia (complication of zoster)

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

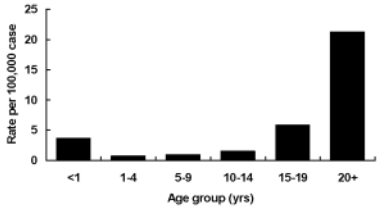
In the prevaccine era, approximately 11,000 persons with varicella required hospitalization each year. Hospitalization rates were approximately 2–3 per 1,000 cases among healthy children and 8 per 1,000 cases among adults. Death occurred in approximately 1 in 60,000 cases. From 1990 through 1996, an average of 103 deaths from varicella were reported each year. Most deaths occur in immunocompetent children and adults. Since 1996, the number of hospitalizations and deaths from varicella has declined more than 90%.

Groups at Increased Risk of Complications of Varicella

- Persons older than 15 years
- Infants younger than 1 year
- Immunocompromised persons
- Newborns of women with rash onset within 5 days before to 2 days after delivery

The risk of complications from varicella varies with age. Complications are infrequent among healthy children. They occur much more frequently in persons older than 15 years of age and infants younger than 1 year of age. For instance,

Varicella Fatality Rate-United States, 1990-1994



*Deaths per 100,000 cases. Meyer et al, *J Infect Dis* 2000;182:383-90

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.

Immunocompromised persons have a high risk of disseminated disease (up to 36% in one report). These persons may have multiple organ system involvement, and the disease may become fulminant and hemorrhagic. The most frequent complications in immunocompromised persons are pneumonia and encephalitis. Children with HIV infection are at increased risk for morbidity from varicella and herpes zoster.

The onset of maternal varicella from 5 days before to 2 days after delivery may result in overwhelming infection of the neonate and a fatality rate as high as 30%. This severe disease is believed to result from fetal exposure to varicella virus without the benefit of passive maternal antibody. Infants born to mothers with onset of maternal varicella 5 days or more prior to delivery usually have a benign course, presumably due to passive transfer of maternal antibody across the placenta.

Zoster

Postherpetic neuralgia, or pain in the area of the ocurrence that persists after the lesions have resolved, is a distressing complication of zoster. There is currently no adequate therapy available. Postherpetic neuralgia may last a year or longer after the episode of zoster. Ocular nerve and other organ involvement with zoster can occur, often with severe sequelae.

Congenital VZV Infection

Primary maternal varicella infection in the first 20 weeks of gestation is occasionally associated with a variety of abnormalities in the newborn, including low birth weight, hypoplasia of an extremity, skin scarring, localized muscular atrophy, encephalitis, cortical atrophy, chorioretinitis, and microcephaly. This constellation of abnormalities, collectively known as congenital varicella syndrome, was first recognized in 1947. The risk of congenital abnormalities from primary maternal varicella infection appears to be very low (less than 2%). Rare reports of congenital birth defects following maternal zoster exist, but virologic confirmation of maternal lesions is lacking.

Congenital Varicella Syndrome

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

Laboratory Diagnosis

Laboratory diagnosis is not routinely required, but is useful if confirmation of the diagnosis or determination of susceptibility is necessary. Varicella incidence has declined dramatically as a result of routine varicella immunization in the United States. This has had the combined effect of increasing the number of atypical cases (either vaccine adverse events or breakthrough wild-type infection in immunized persons) and of reducing physicians' experience in diagnosing varicella. As a result, the need for laboratory confirmation of varicella has increased.

Varicella zoster virus may be isolated in tissue culture. The most frequent source of isolation is vesicular fluid. Laboratory techniques allow differentiation of wild-type and vaccine strains of VZV.

Rapid varicella virus identification techniques are indicated for a case with severe or unusual disease to initiate specific antiviral therapy. VZV polymerase chain reaction (PCR) is the method of choice for rapid clinical diagnosis. Real-time PCR methods are widely available and are the most sensitive and specific method of the available tests. Results are available within several hours. If real-time PCR is unavailable, the direct fluorescent antibody (DFA) method can be used, although it is less sensitive than PCR and requires more meticulous specimen collection and handling.

Specimens are best collected by unroofing a vesicle, preferably a fresh fluid-filled vesicle, and then rubbing the base of a skin lesion with a polyester swab. Crusts from lesions are also excellent specimens for PCR. Other specimen sources such as nasopharyngeal secretions, saliva, blood, urine, bronchial washings, and cerebrospinal fluid are considered less desirable sources than skin lesions because positive test results from such specimens are much less likely. Because viral proteins persist after cessation of viral replication, PCR and DFA may be positive when viral cultures are negative. Additional information concerning virus isolation and strain differentiation can be found at http://www.cdc.gov/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

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)

(RIA), latex agglutination (LA), and enzyme-linked immunosorbent assay (ELISA). ELISA is sensitive and specific, simple to perform, and widely available commercially. A commercially available LA is sensitive, simple, and rapid to perform. LA is generally more sensitive than commercial ELISAs, although it can result in false-positive results, leading to failure to identify persons without evidence of varicella immunity. This latter concern can be minimized by performing LA as a dilution series. Either of these tests would be useful for screening for varicella immunity.

Antibody resulting from vaccination is generally of lower titer than antibody resulting from varicella disease. Commercial antibody assays, particularly the LA test, may not be sensitive enough to detect vaccine-induced antibody in some recipients. Because of the potential for false-negative serologic tests, routine postvaccination serologic testing is not recommended. For diagnosis of acute varicella infection, serologic confirmation would include a significant rise in varicella IgG by any standard serologic assay. Testing using commercial kits for IgM antibody is not recommended since available methods lack sensitivity and specificity; false-positive IgM results are common in the presence of high IgG levels. The National VZV Laboratory at CDC has developed a reliable IgM capture assay. Call 404-639-0066, 404-639-3667, or e-mail vzvlab@cdc.gov for details about collecting and submitting specimens for testing.

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 in tropical areas, varicella infection occurs more commonly among adults than children. The reason(s) for this difference in age distribution are not known with certainty, but may be related to lack of childhood varicella infection in rural populations.

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.

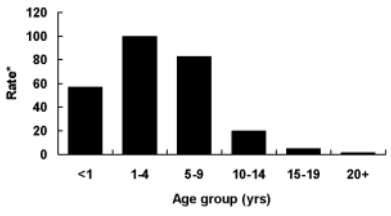
Varicella is highly contagious. It is less contagious than measles, but more so than mumps and rubella. Secondary attack rates among susceptible household contacts of persons with varicella are as high as 90% (that is, 9 of 10 susceptible household contacts of persons with varicella will become infected).

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. The majority of cases (approximately 85%) occurred among children younger than 15 years of age. The highest age-specific incidence of varicella was among children 1–4 years of age, who accounted for 39% of all cases. This age distribution was probably a result of earlier exposure to VZV in preschool and child care settings. Children 5–9 years of age accounted for 38% of cases. Adults 20 years of age and older accounted for only 7% of cases (National Health Interview Survey data, 1990–1994).

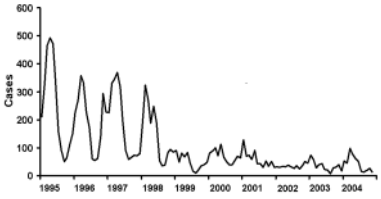
Data from three active varicella surveillance areas indicate that the incidence of varicella, as well as varicella-related hospitalizations, has decreased significantly since licensure of vaccine in 1995. In 2004, varicella vaccination coverage among children 19–35 months in two of the active surveillance areas was estimated to be 89% and 90%. Compared with 1995, varicella cases declined 83%–93% by 2004. Cases declined most among children aged 1–4 and 5–9 years, but a decline occurred in all age groups including infants and adults, indicating reduced transmission of the virus in these groups. The reduction of varicella cases is the result of the increasing use of varicella vaccine. Varicella

Varicella Age-Specific Incidence United States, 1990-1994



*Rate per 100,000 population. National Health Interview Survey data

Varicella Cases by Month Antelope Valley, CA, 1995–2004



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

vaccine coverage among 19–35-month-old children was estimated by the National Immunization Survey to be 88% in 2005.

Varicella in the United States

- Increasing proportion of cases are a result of breakthrough infection
- Outbreaks reported in schools with high varicella vaccination coverage
- Persons with breakthrough infection may transmit virus

Despite high one-dose vaccination coverage and success of the vaccination program in reducing varicella morbidity and mortality, varicella surveillance indicates that the number of reported varicella cases appears to have plateaued. An increasing proportion of cases represent breakthrough infection (chickenpox occurring in a previously vaccinated person). In 2001–2005, outbreaks were reported in schools with high varicella vaccination coverage (96%–100%). These outbreaks had many similarities: all occurred in elementary schools; vaccine effectiveness was within the expected range (72%–85%); the highest attack rates occurred among the younger students; each outbreak lasted about 2 months; and persons with breakthrough infection transmitted the virus although the breakthrough disease was mild. Overall attack rates among vaccinated children were 11%–17%, with attack rates in some classrooms as high as 40%. These data indicate that even in settings where almost everyone was vaccinated and vaccine performed as expected, varicella outbreaks could not be prevented with the current one-dose vaccination policy. These observations led to the recommendation in 2006 for a second routine dose of varicella vaccine.

Herpes Zoster

Herpes zoster is not a notifiable condition. An estimated 500,000 to 1 million episodes of zoster occur annually in the United States. The lifetime risk of zoster is estimated to be at least 20%. Increasing age and cellular immunosuppression are the most important risk factors; 50% of persons living until age 85 years will develop zoster.

Herpes Zoster

- 500,000 to 1 million episodes occur annually in the United States
- Lifetime risk of zoster estimated to be at least 20%
- 50% of persons living until age 85 years will develop zoster

Vaccines Containing Varicella Virus

Three varicella-containing vaccines are now approved for use in the United States: varicella vaccine (Varivax), combination measles-mumps-rubella-varicella (MMRV) vaccine (ProQuad), and herpes zoster vaccine (Zostavax).

Varicella-Containing Vaccines

- Varicella vaccine (Varivax)
  - –approved for persons 12 months and older
- Measles-mumps-rubella-varicella vaccine (ProQuad)
  - –approved for children 12 months through 12 years
- Herpes zoster vaccine (Zostavax)
  - –approved for persons 60 years and older

Characteristics

Varicella Vaccine

Varicella vaccine (Varivax, Merck) is a live attenuated viral vaccine, derived from the Oka strain of VZV. The vaccine virus was isolated by Takahashi in the early 1970s from vesicular fluid from an otherwise healthy child with varicella disease. Varicella vaccine was licensed for general use in Japan and Korea in 1988. It was licensed in the United

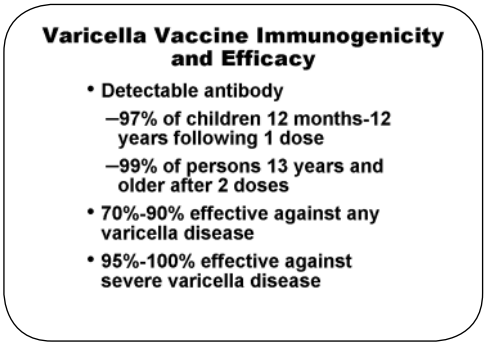
States in 1995 for persons 12 months of age and older. The virus was attenuated by sequential passage in human embryonic lung cell culture, embryonic guinea pig fibroblasts, and in WI-38 human diploid cells. The Oka/Merck vaccine has undergone further passage through MRC-5 human diploid cell cultures for a total of 31 passages. The reconstituted vaccine contains small amounts of sucrose, processed porcine gelatin, sodium chloride, monosodium L-glutamate, sodium diphosphate, potassium phosphate, and potassium chloride, and trace quantities of residual components of MRC-5 cells (DNA and protein), EDTA, neomycin, and fetal bovine serum. The vaccine is reconstituted with sterile water and contains no preservative.

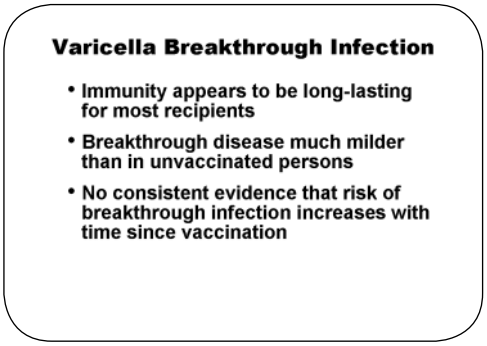
Measles-Mumps-Rubella-Varicella Vaccine

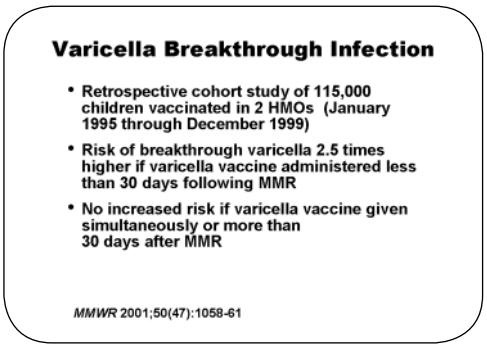
In September 2005, the Food and Drug Administration (FDA) licensed a combined live attenuated measles-mumps-rubella and varicella vaccine (ProQuad, Merck) for use in persons 12 months through 12 years of age. The attenuated measles, mumps, and rubella vaccine viruses in MMRV are identical and of equal titer to those in the measles-mumps-rubella (MMR) vaccine. The titer of Oka/Merck varicella zoster virus is higher in MMRV vaccine than in single-antigen varicella vaccine, a minimum of 9,772 (3.99 $\log^{10}$) plaque-forming units (PFU) versus 1,350 PFU (~3.13 $\log^{10}$), respectively. Each 0.5-mL dose contains a small quantity of sucrose, hydrolyzed gelatin, sodium chloride, sorbitol, monosodium L-glutamate, sodium phosphate dibasic, human albumin, sodium bicarbonate, potassium phosphate monobasic, potassium chloride; potassium phosphate dibasic; residual components of MRC-5 cells (DNA and protein) neomycin, bovine calf serum, and other buffer and media ingredients. The vaccine is reconstituted with sterile water and contains no preservative.

Herpes Zoster Vaccine

In May 2006, the FDA approved herpes zoster vaccine (Zostavax, Merck) for use in persons 60 years of age and older. The vaccine contains the same Oka/Merck varicella zoster virus used in varicella and MMRV vaccines but at a much higher titer (a minimum of 19,400 PFU versus 1,350 PFU in varicella vaccine). Each 0.65-mL dose contains a small amount of sucrose, hydrolyzed porcine gelatin, sodium chloride, monosodium L-glutamate, sodium phosphate dibasic, potassium phosphate monobasic, potassium chloride; residual components of MRC-5 cells including (DNA and protein); neomycin and bovine calf serum. The vaccine is reconstituted with sterile water and contains no preservative.







Immunogenicity and Vaccine Efficacy

Varicella Vaccine

After one dose of single-antigen varicella vaccine, 97% of children 12 months to 12 years of age develop detectable antibody titers. More than 90% of vaccine responders 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 90%–100% against moderate or severe disease.

Among healthy adolescents and adults 13 years of age and older, an average of 78% develop antibody after one dose, and 99% develop antibody after a second dose given 4 to 8 weeks later. Antibody persisted for at least 1 year in 97% of vaccinees after the second dose given 4 to 8 weeks after the first dose. Studies on the persistence of antibody and clinical efficacy in both children and adults are ongoing.

Immunity appears to be long-lasting, and is probably permanent in the majority of vaccinees. Breakthrough infection is significantly milder, with fewer lesions (generally fewer than 50), many of which are maculopapular rather than vesicular. Most persons with breakthrough infection do not have fever.

Although findings of some studies have suggested otherwise, most investigations have not identified time since vaccination as a risk factor for breakthrough varicella. Some, but not all, recent investigations have identified the presence of asthma, use of steroids, and vaccination at younger than 15 months of age as risk factors for breakthrough varicella. Breakthrough varicella infection could be a result of several factors, including interference of vaccine virus replication by circulating antibody, impotent vaccine resulting from storage or handling errors, or inaccurate recordkeeping.

Interference from live viral vaccine administered before varicella vaccine could also reduce vaccine effectiveness. A study of 115,000 children in two health maintenance organizations during 1995–1999 found that children who received varicella vaccine less than 30 days after MMR vaccination had a 2.5-fold increased risk of breakthrough varicella compared with those who received varicella vaccine before, simultaneously with, or more than 30 days after MMR. 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.

MMRV Vaccine

MMRV vaccine was licensed on the basis of equivalence of immunogenicity of the antigenic components rather than

the clinical efficacy. Clinical studies involving healthy children age 12–23 months indicated that those who received a single dose of MMRV vaccine developed similar levels of antibody to measles, mumps, rubella and varicella as children who received MMR and varicella vaccines concomitantly at separate injection sites.

Herpes Zoster Vaccine

The primary clinical trial for zoster vaccine included more than 38,000 adults 60 to 80 years of age with no history of prior shingles. Participants were followed for a median of 3.1 years after a single dose of vaccine. Compared with the placebo group, the vaccine group had 51% fewer episodes of zoster. Efficacy was highest for persons 60–69 years of age (64%) and declined with increasing age. Efficacy was 18% for participants 80 years or older. Vaccine recipients who developed zoster generally had less severe disease. Vaccine recipients also had about 66% less postherpetic neuralgia, the pain that can persist long after the shingles rash has resolved. The duration of reduction of risk of zoster is not known.

Herpes Zoster Vaccine Efficacy

- Compared with placebo group vaccine group had:
  - —51% fewer episodes of zoster
  - —Lower efficacy for older recipients
  - —Less severe disease
  - —66% less postherpetic neuralgia

NEJM 2005;352(22):2271-84.

Vaccination Schedule and Use

Varicella Vaccine

As of January 2007, ACIP recommendations for a second dose of varicella vaccine have not been published. Recommendations included here are provisional until published in *Morbidity and Mortality Weekly Report*. Publication of these recommendations is expected by mid-2007.

Varicella virus vaccine is recommended for all children without contraindications at 12 through15 months of age. The vaccine may be given to all children at this age regardless of prior history of varicella. However, vaccination is not necessary for children with reliable histories of chickenpox.

In June 2006, the Advisory Commitee on Immunization Practices (ACIP) voted to recommend a routine second dose of varicella vaccine. The second dose should be administered at 4 through 6 years of age, at the same visit as the second dose of MMR vaccine. The second dose may be administered earlier than 4 through 6 years of age if at least 3 months have elapsed following the first dose (i.e., the minimum interval between doses of varicella vaccine for children younger than 13 years is 3 months). However, if the second dose is administered at least 28 days following the first dose, the second dose does not need to be repeated. A second dose of varicella vaccine is also recommended for persons older than 4 through 6 years of age who have

Varicella Vaccine Recommendations Children

- Routine vaccination at 12-15 months of age
- Routine second dose at 4-6 years of age*
- Minimum interval between doses of varicella vaccine for children younger than 13 years of age is 3 months

*provisional recommendation as of January 2007

received only one dose. Varicella vaccine doses administered to persons younger than 13 years should be separated by at least 3 months.

Varicella vaccine is also recommended for all children without evidence of varicella immunity (see Varicella Immunity section) 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 and complications are more frequent.

All varicella-containing vaccines should be administered by the subcutaneous route. Varicella vaccine has been shown to be safe and effective in healthy children when administered at the same time as MMR vaccine at separate sites and with separate syringes. If varicella and MMR vaccines are not administered at the same visit, they should be separated by at least 28 days. Varicella vaccine may also be administered simultaneously (but at separate sites with separate syringes) with all other childhood vaccines. ACIP strongly recommends that varicella vaccine be administered simultaneously with all other vaccines recommended at 12 through 15 months of age.

Children with a clinician-diagnosed or verified history of typical chickenpox can be assumed to be immune to varicella. Serologic testing of such children prior to vaccination is not warranted because the majority of children between 12 months and 12 years of age without a clinical history of chickenpox are not immune. Prior history of chickenpox is not a contraindication to varicella vaccination.

Varicella Vaccine Recommendations Adolescents and Adults

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

Varicella vaccine should be administered to all adolescents and adults 13 years of age and older who do not have evidence of varicella immunity (see Varicella Immunity section). Persons 13 years of age and older should receive two doses of varicella vaccine separated by at least 4 weeks. If there is a lapse of more than 4 weeks after the first dose, the second dose may be administered at any time without repeating the first dose.

Varicella Vaccine Recommendations Healthcare Personnel

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

Assessment of varicella immunity status of all adolescents and adults and vaccination of those who lack evidence of varicella immunity are desirable to protect these individuals from the higher risk of complications from acquired varicella. Vaccination may be offered at the time of routine healthcare visits. However, specific assessment efforts should be focused on adolescents and adults who are at highest risk of exposure and those most likely to transmit varicella to others.

The ACIP recommends that all healthcare personnel be immune to varicella. In healthcare settings, serologic screening

of personnel who are uncertain of their varicella history, or who claim not to have had the disease is likely to be cost-effective. Testing for varicella immunity following two oses of vaccine is not necessary because 99% of persons are seropositive after the second dose. Moreover, available commercial assays are not sensitive enough to detect antibody following vaccination in all instances.

Seroconversion does not always result in full protection against disease, although no data regarding correlates of protection are available for adults. If a vaccinated healthcare provider is exposed to VZV, the employee should be monitored daily from day 10 to day 21 after exposure through the employee health or infection control program to determine clinical status (screen for fever, skin lesions, and systemic symptoms). Persons with varicella may be infectious starting 2 days before rash onset. In addition, the healthcare 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.

The risk of transmission of vaccine virus from a vaccinated person to a susceptible contact appears to be very low (see Transmission of Varicella Vaccine Virus section), and the benefits of vaccinating susceptible healthcare providers clearly outweigh this potential risk. Transmission of vaccine virus appears to occur primarily if and when the vaccinee develops a vaccine-associated rash. As a safeguard, institutions may wish to consider protocols for personnel who develop a rash following vaccination (e.g., avoidance of contact with persons at high risk of serious complications, such as immunosuppressed persons who do not have evidence of varicella immunity).

MMRV Vaccine

MMRV vaccine is indicated for vaccination against measles, mumps, rubella and varicella in children 12 months through 12 years of age. Persons 13 years of age and older should not receive MMRV. Use of licensed combination vaccines, such as MMRV, is preferred to separate injection of their 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. MMRV may be used for both the first and second doses of MMR and varicella in children younger than 13 years. The minimum interval between doses of MMRV is 3 months. However, if the second dose is administered at least 28 days following the first dose, the second dose does not need to be repeated.

MMRV Vaccine

- Approved for children 12 months through 12 years of age (to age 13 years)
- Do not use for persons 13 years and older
- May be used for both first and second doses of MMR and varicella vaccines
- Minimum interval between doses is 3 months

Herpes Zoster Vaccine

As of January 2007, ACIP recommendations for the use of herpes zoster varicella vaccine have not been published. Recommendations included here are provisional until published in *Morbidity and Mortality Weekly Report*. Publication of these recommendations is expected by mid-2007.

Herpes Zoster Vaccine*

- Approved for a single dose among persons 60 years and older
- May vaccinate regardless of prior history of herpes zoster (shingles)
- Persons with a chronic medical condition may be vaccinated unless a contraindication or precaution exists for the condition

*provisional recommendations as of January 2007

Zoster vaccine is approved by FDA for persons 60 years and older. A single dose of zoster vaccine is recommended for adults 60 years of age and older whether or not they report a prior episode of herpes zoster. Persons with a chronic medical condition may be vaccinated unless a contraindication or precaution exists for the condition (see Conraindications and Precautions to Vaccination).

Postexposure Prophylaxis

Varicella Vaccine 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 administered more than 5 days after exposure but will produce immunity if not infected

Varicella Vaccine

Data from the United States and Japan in a variety of settings indicate that varicella vaccine is 70% to 100% effective in preventing illness or modifying the severity of illness if used within 3 days, and possibly up to 5 days, after exposure. ACIP recommends the vaccine for use in persons who do not have evidence of varicella immunity following exposure to varicella. If exposure to varicella does not cause infection, postexposure vaccination should induce protection against subsequent exposure. If the exposure results in infection, there is no evidence that administration of varicella vaccine during the incubation period or prodromal stage of illness increases the risk for vaccine-associated adverse reactions. Although postexposure use of varicella vaccine has potential applications in hospital settings, preexposure vaccination of all healthcare workers without evidence of varicella immunity is the recommended and preferred method for preventing varicella in healthcare settings.

Varicella outbreaks in some settings (e.g., child care facilities and schools) can persist up to 6 months. Varicella vaccine has been used successfully to control these outbreaks. The ACIP recommends a second dose of varicella vaccine for outbreak control. During a varicella outbreak, persons who have received one dose of varicella vaccine should receive a second dose, provided the appropriate vaccination interval has elapsed since the first dose (3 months for persons aged 12 months to 12 years and at least 4 weeks for persons aged 13 years of age and older).

MMRV Vaccine

MMRV vaccine may be used as described for varicella vaccine, and for measles as described in Chapter 10, Measles.

Herpes Zoster Vaccine

Exposure to a person with either primary varicella (chickenpox) or herpes zoster does not cause zoster in the exposed person. Herpes zoster vaccine has no role in the postexposure management of either chickenpox or zoster and should not be used for this purpose.

Varicella Immunity

In 2006, the ACIP approved a revised definition for evidence of immunity to varicella (as of January 2007 this recommendation has not yet been published, but will be published with the two-dose vaccine recommendation by mid-2007). Evidence of immunity to varicella includes any of the following:

- Documentation of age-appropriate vaccination:
  - Preschool-aged children 12 months of age or older: one dose
  - School-aged children, adolescents, and adults: two doses
- Laboratory evidence of immunity or laboratory confirmation of disease. Commercial assays can be used to assess disease -induced immunity, but they lack adequate sensitivity to reliably detect vaccine-induced immunity (i.e., they may yield false-negative results).
- Born in the United States before 1980. For healthcare providers and pregnant women, birth before 1980 should not be considered evidence of immunity. Persons born outside the United States should meet one of the other criteria for varicella immunity.
- A healthcare provider diagnosis or verification of varicella disease. Verification of history or diagnosis of typical disease can be done by any healthcare provider (e.g., school or occupational clinic nurse, nurse practitioner, physician assistant, physician). For persons reporting a history of or presenting with atypical and/or mild cases, assessment by a physician or designee is recommended, and one of the following should be sought: a) an epidemiologic link to a typical varicella case, or b) evidence of laboratory confirmation if laboratory testing was performed at the time of acute disease. When such documentation is lacking, a person should not be considered as having a valid history of disease, because other diseases may mimic mild atypical varicella.
- History of herpes zoster based on healthcare provider diagnosis.

Varicella Immunity*

- Written documentation of age-appropriate vaccination
- Laboratory evidence of immunity or laboratory confirmation of disease
- Born in the United States before 1980
- Healthcare provider diagnosis or verification of varicella disease
- History of herpes zoster based on healthcare provider diagnosis

*provisional recommendations as of January 2007

Adverse Reactions Following Vaccination

Varicella Vaccine

The most common adverse reactions following varicella vaccine are local reactions, such as pain, soreness, erythema,

Varicella Vaccine Adverse Reactions

- Local reactions (pain, erythema)
  - —19% (children)
  - —24% (adolescents and adults)
- Generalized rash – 4%-6%
  - —may be maculopapular rather than vesicular
  - —average 5 lesions
- Systemic reactions not common
- Adverse reactions similar for MMRV

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 3% of children and by 1% of adolescents and adults following the second dose. In both circumstances, a median of two lesions have been present. These lesions generally occur within 2 weeks, and are most commonly maculopapular rather than vesicular. A generalized varicella-like rash is reported by 4%–6% of recipients of varicella vaccine (1% after the second dose in adolescents and adults), with an average of five lesions. Most of these generalized rashes occur within 3 weeks and most are maculopapular.

Systemic reactions are not common. Fever within 42 days of vaccination is reported by 15% of children and 10% of adolescents and adults. The majority of these episodes of fever have been attributed to concurrent illness rather than to the vaccine.

Zoster Following Vaccination

- Most cases in children
- Not all cases caused by vaccine virus
- Risk from vaccine virus less than from wild-type virus
- Usually a mild illness without complications such as postherpetic neuralgia

Varicella vaccine is a live virus vaccine and may result in a latent infection, similar to that caused by wild varicella virus. Consequently, zoster caused by the vaccine virus has been reported, mostly among vaccinated children. Not all these cases have been confirmed as having been caused by vaccine virus. The risk of zoster following vaccination appears to be less than that following infection with wild-type virus. The majority of cases of zoster following vaccine have been mild and have not been associated with complications such as postherpetic neuralgia.

MMRV Vaccine

The clinical trial of MMRV compared events that occurred within 42 days of receiving either MMRV or MMR and varicella vaccine separately in different anatomic sites. The frequencies of local reactions and generalized varicella-like rash were similar to those described for varicella vaccine. A temperature of 102°F or higher within 42 days of vaccination was more common in the MMRV group (22%) than in the group that received MMR and varicella vaccine at different sites (15%). A measles-like rash also occurred more frequently in MMRV recipients (3%) than in the group receiving separate injections (2.1%). Both fever and measles-like rash usually occurred 5–12 days following vaccination.

Herpes Zoster Vaccine Adverse Reactions

- Local reactions – 34% (pain, erythema)
- No increased risk of fever
- No serious adverse reactions identified

Herpes Zoster Vaccine

In the largest clinical trial of zoster vaccine, local reactions (erythema, pain or tenderness, and swelling) were the most common adverse reaction reported by vaccine recipients

(34%), and were reported more commonly than by placebo recipients (6%). A temperature of 101°F or higher within 42 days of vaccination occurred at a similar frequency among both vaccine (0.8%) and placebo (0.9%) recipients. No serious adverse reactions were identified during the trial.

Contraindications and Precautions to Vaccination

Contraindications and precautions are similar for all varicella-containing vaccines. Persons with a severe allergic reaction (anaphylaxis) to a vaccine component or following a prior dose of vaccine should not receive varicella vaccine. Varicella, MMRV, and zoster vaccines all contain minute amounts of neomycin and hydrolyzed gelatin but do not contain egg protein or preservative.

Varicella-Containing Vaccines Contraindications and Precautions

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

Persons with immunosuppression due to leukemia, lymphoma, generalized malignancy, immune deficiency disease, or immunosuppressive therapy should not be vaccinated with a varicella-containing vaccine. However, treatment with low-dose (less than 2 mg/kg/day), alternate-day, topical, replacement, or aerosolized steroid preparations is not a contraindication to vaccination. Persons whose immunosuppressive therapy with steroids has been discontinued for 1 month (3 months for chemotherapy) may be vaccinated.

Single-antigen varicella vaccine may be administered to persons with impaired humoral immunity (e.g., hypogammaglobulinemia). However, the blood products used to treat humoral immunodeficiency may interfere with the response to vaccination. Recommended spacing between administration of the blood product and receipt of varicella vaccine should be observed (see Chapter 2, General Recommendations on Immunization, for details).

Varicella-Containing Vaccines Use in Immunocompromised Persons

- Most immunocompromised persons should not receive varicella-containing vaccines
- Varicella vaccine may be administered to persons with isolated humoral immunodeficiency
- Consider varicella vaccination for HIV-infected children with CD4% of 15% or higher

Persons with moderate or severe cellular immunodeficiency resulting from infection with human immunodeficiency virus (HIV), including persons diagnosed with acquired immunodeficiency syndrome (AIDS) should not receive varicella vaccine. HIV-infected children with CD4 T-lymphocyte percentage of 15% or higher may be considered for vaccination. These children may receive MMR and single-antigen varicella vaccines, but they should not receive MMRV. Zoster vaccine should not be administered to persons who are immunosuppressed for any reason.

Varicella VaccineUse in Immunocompromised Persons

- MMRV not approved for use in persons with HIV infection
- Do not administer zoster vaccine to immunosuppressed persons

Women known to be pregnant or attempting to become pregnant should not receive a varicella-containing vaccine. To date, no adverse outcomes of pregnancy or in a fetus have been reported among women who inadvertently received varicella vaccine shortly before or during pregnancy. Although the manufacturer's package insert states otherwise,

ACIP recommends that pregnancy be avoided for 1 month following receipt of varicella vaccine.

The ACIP recommends prenatal assessment and postpartum vaccination for varicella. Women should be assessed during a prenatal healthcare visit for evidence of varicella immunity. Upon completion or termination of pregnancy, women who do not have evidence of varicella immunity should receive the first dose of varicella vaccine before discharge from the healthcare facility. The second dose should be administered at least 4 weeks later at the postpartum or other healthcare visit. Standing orders are recommended for healthcare settings where completion or termination of pregnancy occurs to ensure administration of varicella vaccine.

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.

Varicella Vaccination in Pregnancy Registry

800.986.8999

Vaccination of persons with moderate or severe acute illnesses should be postponed until the condition has improved. This precaution is intended to prevent complicating the management of an ill patient with a potential vaccine adverse event, such as fever. Minor illness, such as otitis media and upper respiratory infections, concurrent antibiotic therapy, and exposure or recovery from other illnesses are not contraindications to varicella vaccine. Although there is no evidence that either varicella or varicella vaccine exacerbates tuberculosis, vaccination is not recommended for persons known to have untreated active tuberculosis. Tuberculosis skin testing is not a prerequisite for varicella vaccination.

The effect of the administration of antibody-containing blood products (e.g., immune globulin, whole blood or packed red blood cells, or intravenous immune globulin) on the response to varicella vaccine virus is unknown. Because of the potential inhibition of the response to varicella vaccination by passively transferred antibodies, varicella or MMRV vaccine should not be administered for 3–11 months after receipt of antibody-containing blood products. ACIP recommends applying the same intervals used to separate antibody-containing products and MMR to varicella vaccine (see chapter 2, General Recommendations on Immunization, and Appendix A for additional details). Immune globulin should not be given for 3 weeks following vaccination unless the benefits exceed those of the vaccine. In such cases, the vaccinees should either be revaccinated or tested for immunity at least 3 months later (depending on the antibody-containing product administered) and revaccinated if seronegative.

Recent receipt of an antibody-containing blood product is not a precaution to use of herpes zoster vaccine.

No adverse events following varicella vaccination related to the use of salicylates (e.g., aspirin) have been reported to date. However, the manufacturer recommends that vaccine recipients avoid the use of salicylates for 6 weeks after receiving varicella or MMRV vaccine because of the association between aspirin use and Reye syndrome following chickenpox.

Transmission of Varicella Vaccine Virus

Available data suggest that transmission of varicella vaccine virus is a rare event. Instances of suspected secondary transmission of vaccine virus have been reported, but in few instances has the secondary clinical illness been shown to be caused by vaccine virus. Several cases of suspected secondary transmission have been determined to have been caused by wild varicella virus. In studies of household contacts, several instances of asymptomatic seroconversion have been observed. It appears that transmission occurs mainly, and perhaps only, when the vaccinee develops a rash. If a vaccinated child develops a rash, it is recommended that close contact with persons who do not have evidence of varicella immunity and who are at high risk of complications of varicella, such as immunocompromised persons, be avoided until the rash has resolved.

Transmission of varicella vaccine virus from recipients of zoster vaccine has not been reported.

Transmission of Varicella Vaccine Virus

- Transmission of vaccine virus is a rare event
- Transmission appears to occur only if the vaccinee develops a rash
- Transmission of vaccine virus from recipients of zoster vaccine has not been reported

Vaccine Storage and Handling

Varicella vaccine is very fragile, and all vaccines that contain it must be handled with extreme care. To maintain potency, all varicella-containing vaccines must be stored frozen at an average temperature of 5°F (-15°C). Household freezers, including frost-free models, manufactured since the mid-1990s are acceptable for storage of these vaccines. Refrigerators with ice compartments that are not tightly enclosed or are enclosed with unsealed, uninsulated doors (i.e., small dormitory-style refrigerator/freezer combinations) are not capable of maintaining the required storage temperature. Regardless of the type of freezer, providers should check the adequacy of their freezer storage before obtaining vaccine by monitoring and verifying the temperature of their freezer.

The vaccine diluent should be stored separately at room temperature or in the refrigerator. The vaccine should be reconstituted according to the directions in the package insert and only with the diluent supplied (or with the diluent

Varicella-Containing Vaccine Storage and Handling

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

supplied for MMR vaccine), which does not contain preservative or other antiviral substances that might inactivate the vaccine virus. Once reconstituted, all varicella-containing vaccines must be used immediately to minimize loss of potency. The vaccine must be discarded if not used within 30 minutes of reconstitution.

Varicella Vaccine Information

800-9VARIVAX

If varicella vaccine (but not MMRV or zoster 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 varicella 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. MMRV and zoster vaccines cannot be stored at refrigerator temperature at any time. 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 properly insulated container should be used, the vaccine should be transported on dry ice, and the temperature should be monitored continuously, to ensure that the appropriate storage temperature is maintained (see Appendix C).

Varicella Zoster Immune Globulin

In 2004, the only U.S.-licensed manufacturer of varicella zoster immune globulin (VZIG) (Massachusetts Public Health Biologic Laboratories, Boston, Massachusetts) discontinued production of VZIG. The supply of the licensed VZIG product was depleted in early 2006. In February 2006, an investigational (not licensed) VZIG product, VariZIG (Cangene Corporation, Winnipeg, Canada) became available under an investigational new drug application (IND) submitted to the FDA. This product can be requested from the sole authorized U.S. distributor, FFF Enterprises (Temecula, California), for patients who have been exposed to varicella and who are at increased risk for severe disease and complications.

The investigational VariZIG, similar to licensed VZIG, is a purified human immune globulin preparation made from plasma containing high levels of anti-varicella antibodies (immunoglobulin class G [IgG]). Unlike the previous product,

the investigational product is lyophilized. When properly reconstituted, VariZIG is approximately a 5% solution of IgG that can be administered intramuscularly. As with any product used under IND, patients must be informed of potential risks and benefits and must give informed consent before receiving the product.

Patients without evidence of immunity to varicella (i.e., without history of disease or age-appropriate vaccination) who are at high risk for severe disease and complications, who have been exposed to varicella, and from whom informed consent has been obtained, are eligible to receive the IND application product under an expanded access protocol. The patient groups recommended by ACIP to receive VariZIG include the following:

- Immunocompromised patients
- Neonates whose mothers have signs and symptoms of varicella around the time of delivery (i.e., 5 days before to 2 days after)
- Preterm infants born at 28 weeks gestation or later who are exposed during the neonatal period and whose mothers do not have evidence of immunity
- Preterm infants born earlier than 28 weeks' gestation or who weigh 1,000g or less at birth and were exposed during the neonatal period, regardless of maternal history of varicella disease or vaccination
- Pregnant women

Addition information concerning the acquisition and use of this product is available in the March 3, 2006, edition of *Morbidity and Mortality Weekly Report*, available at http://www.cdc.gov/MMWR/preview/MMWRhtml/mm5508a5.htm

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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 or higher), formalin, chlorine

Pathogenesis

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

Hepatitis A Pathogenesis

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

Hepatitis A

Hepatitis A Clinical Features

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

Clinical Features

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

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

Complications

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 IgM anti-HAV. Acute HAV infection is confirmed during the acute or early convalescent phase of infection by the presence of IgM anti-HAV in serum. IgM generally becomes detectable 5–10 days before the onset of symptoms and can persist for up to 6 months.

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

IgM anti-HAV. Persons who are total anti-HAV positive and IgM anti-HAV negative have serologic markers indicating immunity consistent with either past infection or vaccination.

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

Medical Management

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

Epidemiology

Occurrence

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

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

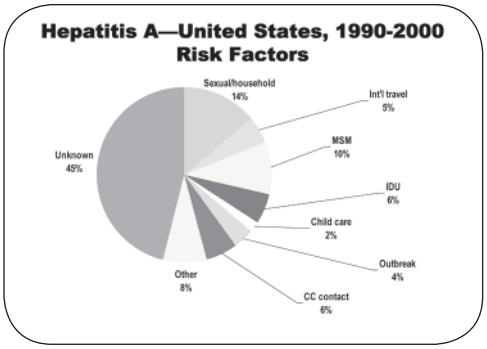
There is no appreciable seasonal variation in hepatitis A incidence.

Communicability

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

Hepatitis A Epidemiology

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



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

Risk Factors

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

Groups at increased risk for hepatitis A or its complications include international travelers, men who have sex with men, and users of illegal drugs. Outbreaks of hepatitis A have also been reported among 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

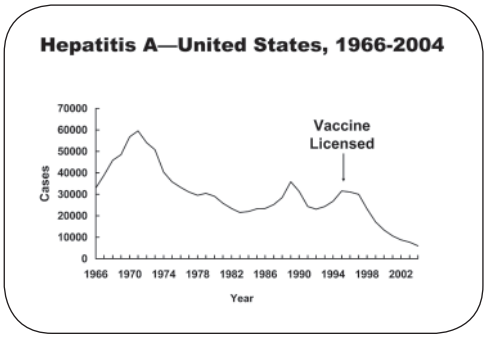
In the United States, hepatitis A has occurred in large nationwide epidemics approximately every 10 years, with the last increase in cases in 1989. However, between epidemics HAV infection continues to occur at relatively high rates. Hepatitis A became nationally reportable as a distinct entity in 1966. 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.

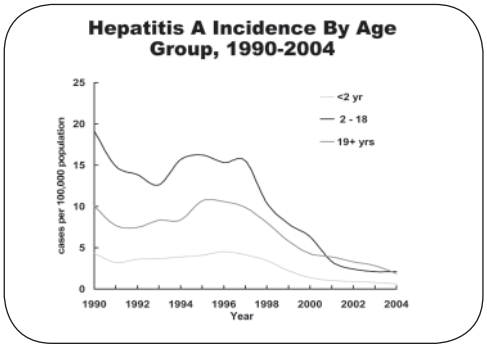
Historically, children 2–18 years of age have had the highest rates of hepatitis A (15–20 cases per 100,000 population in the early to mid-1990s). Since 2002, rates among children have declined and the incidence of hepatitis A is now similar in all age groups.

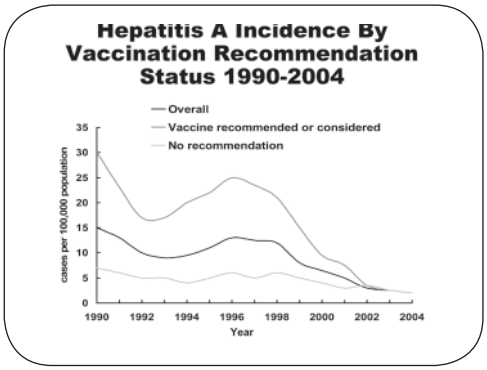
Based on testing from phase 1 of the Third National Health and Nutrition Examination Survey (NHANES III) conducted during 1988–1994, the prevalence of total antibody to HAV (anti-HAV) among the general U.S. population is 33%. Seroprevalence of HAV antibody increases with age, from 9% among 6–11-year-olds 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







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 IgM anti-HAV.

Hepatitis A Vaccine

Characteristics

Hepatitis A Vaccines

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

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

Immunogenicity and Vaccine Efficacy

Hepatitis A Vaccine Immunogenicity

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

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

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

Both vaccines are highly effective in preventing clinical hepatitis A. The efficacy of HAVRIX in protecting against clinical hepatitis A was 94% among 40,000 Thai children 1–16 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.

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

- 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

MMWR 2006;55(No.RR-7):1-23

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.

ACIP Recommendation for Routine Hepatitis A Vaccination of Children

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

MMWR 2006;55(No.RR-7):1-23

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

HAVRIX is available in two formulations: pediatric (720 ELISA units [EL.U.] per 0.5-mL dose) and adult (1,440 EL.U. per 1.0-mL dose). Children 1 through 18 years of age should receive a single primary dose of the pediatric formulation followed by a booster dose 6–12 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	1-18 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 through 18 years of age should receive one dose of pediatric formulation (25 U per dose) with a booster dose 6–18 months later. Adults 19 years of age and older should receive one dose of adult formulation (50 U per dose) with a booster dose 6–18 months after the first dose. The vaccine should be administered intramuscularly into the deltoid muscle. A needle length appropriate for the vaccinee's age and size should be used (minimum of 1 inch).

Recommended Doses of VAQTA® Hepatitis A Vaccine

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

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

Hepatitis A Vaccines

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

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 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.

Twinrix

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

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

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

Hepatitis A Vaccine Recommendations

- Travelers to high- or intermediate-risk countries
- Protected by 4 weeks after dose
- For optimal protection, immune globulin also may be administered to persons traveling to high-risk areas less than 4 weeks after the initial dose

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 4 weeks after receiving the first dose of vaccine. Persons administered single-antigen hepatitis A vaccine often will have detectable anti-HAV antibody by 2 weeks after the first dose. The proportion of persons who have detectable anti-HAV antibody at 2 weeks might be lower after a single dose of Twinrix because of the lower dose of hepatitis A antigen in this product.

Because protection might not be complete until 4 weeks after vaccination, for optimal protection, persons traveling to an area in which risk is high less than 4 weeks after the initial dose also may be administered immune globulin (IG) (0.02 mL/kg), at a different anatomic injection site. Travelers departing in less than 4 weeks who do not or cannot receive IG should receive hepatitis A vaccine and be informed that they might not be protected from HAV infection in the subsequent 2 to 4 weeks. Travelers who choose not to receive vaccine should receive a single dose of IG (0.02 mL/kg), which provides protection against HAV infection for up to 3 months. Persons whose travel period is more than 2 months should be administered IG at 0.06 mL/kg. IG should be repeated in 5 months for prolonged travel.

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

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

Hepatitis A vaccination is not routinely recommended for healthcare 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 for hepatitis A

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

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

Hepatitis A Vaccine Contraindications and Precautions

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

component or following a prior dose of hepatitis A vaccine, hypersensitivity to alum or, in the case of HAVRIX, to the preservative 2-phenoxyethanol. Vaccination of persons with moderate or severe acute illnesses should be deferred until the person's condition has improved.

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

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. 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 80%–90% 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 3–5 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.)

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Hepatitis A

14



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.

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

Hepatitis B

- 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

Hepatitis B Virus

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

Hepatitis B Virus

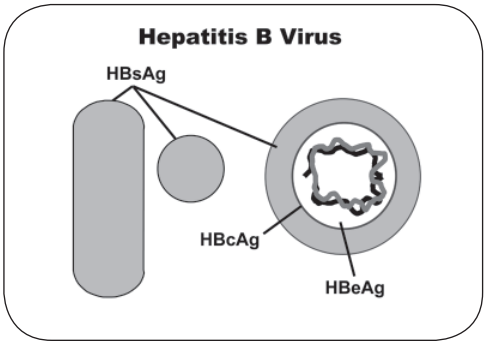
- Hepadnaviridae family (DNA)
- Numerous antigenic components
- Humans are only known host
- May retain infectivity for more than 7 days at room temperature

HBV is the most common known cause of chronic viremia, with more than 350 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. The World Health Organization estimates that more than 600,000 persons died worldwide in 2002 of hepatitis B-associated acute and chronic liver disease.

Hepatitis B Virus Infection

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

Hepatitis B



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

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

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

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

Complications

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

Hepatitis B Complications

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

Chronic HBV Infection

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

Chronic Hepatitis B Virus Infection

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

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

Risk of Chronic HBV Carriage by Age of Infection



Laboratory Diagnosis

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

HBsAg is the most commonly used test for diagnosing acute HBV infections or detecting carriers. HBsAg can be detected

as early as 1 or 2 weeks and as late as 11 or 12 weeks after exposure to HBV when sensitive assays are used. The presence of HBsAg indicates that a person is infectious, regardless of whether the infection is acute or chronic.

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

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

Interpretation of Hepatitis B Serologic Tests

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

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

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

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

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

Medical Management

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

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

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

Epidemiology

Reservoir

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

Hepatitis B Epidemiology

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

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

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

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

Hepatitis B Perinatal Transmission*

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

*in the absence of postexposure prophylaxis

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

Global Patterns of Chronic HBV Infection

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

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

In China, Southeast Asia, most of Africa, most Pacific Islands, parts of the Middle East, and the Amazon Basin, 8% to 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 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.

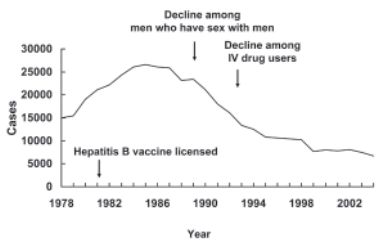
The incidence of reported hepatitis B peaked in the mid-1980s, with about 26,000 cases reported each year. Reported cases have declined since that time, and fell below 10,000 cases for the first time in 1996. The decline in cases during the 1980s and early 1990s is generally attributed to reduction of 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 5,119 cases of hepatitis B were reported in 2005.

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

Hepatitis B—United States, 1978-2004

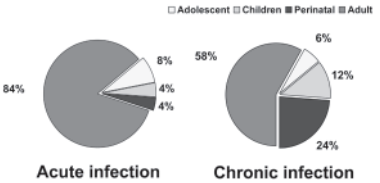


HBV Disease Burden in the United States*

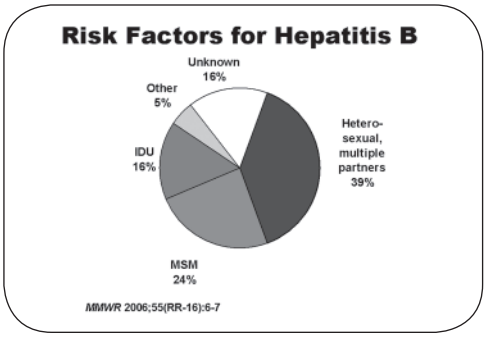
New infections	78,000/yr
Current carriers	>1 million
New carriers	>5,000/yr
Death	5,000/yr

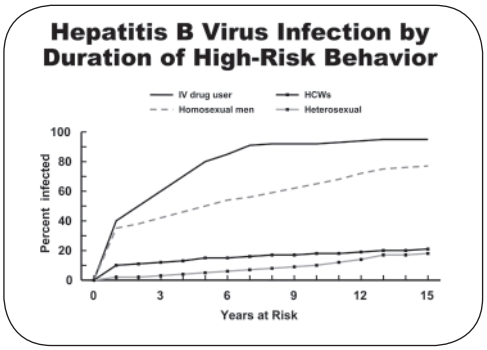
*2001 estimates

Age of Infection of Acute and Chronic Hepatitis B Virus Infection



CDC Sentinel Sites. 1989 data.





disproportionate 24% of chronic infections.
In the United States in 2005, the highest incidence of acute hepatitis B was among adults aged 25–45 years. Approximately 79% of persons with newly acquired hepatitis B infection are known to engage in high-risk sexual activity or injection-drug use. Other known exposures (i.e., occupational, household, travel, and healthcare-related) together account for 5% of new infections. Approximately 16% of persons deny a specific risk factor for infection.

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

Prevalence of Hepatitis B in Various Population Groups

	Population Group	Prevalence of Serologic Markers of HBV Infection	
		HBsAg (%)	All Markers (%)
High-Risk	Immigrants/refugees from areas of high HBV endemicity.	13	70-85
	Clients in 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. Recommendations to further enhance vaccination of adults at increased risk of HBV infection were published in 2006.

Strategy to Eliminate Hepatitis B Virus Transmission—United States

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

Hepatitis B Vaccine

Characteristics

A plasma-derived vaccine was licensed in the United States in 1981. It was produced from 22-nm HBsAg particles purified from the plasma of 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: at least 20 years
- Schedule: 3 Doses
- Booster doses not routinely recommended

Hepatitis B Vaccine Formulations

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

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

Hepatitis B vaccine is produced by two manufacturers in the United States, Merck (Recombivax HB) and GlaxoSmithKline Pharmaceuticals (Engerix-B). Both vaccines are available in both pediatric and adult formulations. Although the antigen content of the vaccines differs, vaccines made by different manufacturers are interchangeable, except for the two-dose schedule for adolescents aged 11–15 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 20 years following immunization, and both adults and children with declining antibody levels are still protected against significant HBV infection (i.e., clinical disease, HBsAg antigenemia, or significant elevation of liver enzymes). Exposure to HBV results in an anamnestic anti-HBs response that prevents clinically significant HBV infection. Chronic HBV infection has only rarely been documented among vaccine responders.

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 last (third or fourth) dose by 6 months of age (12–15 months if Comvax is used).

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 before 6 weeks of age
- May be used in infants whose mothers are HBsAg positive or status is unknown

Comvax is licensed for use at 2, 4, and 12–15 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.

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 1.0-mL (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.

Hepatitis B Vaccine
Adolescent and Adult Schedule

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

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

Alternative Adolescent Vaccination Schedule

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

Adults (20 Years of Age and Older)

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

The usual schedule for adults is two doses separated by no less than 4 weeks, and a third dose 4–6 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.

Adults at Risk for HBV Infection

- Sexual exposure
  - —sex partners of HBsAg-positive persons
  - —sexually active persons not in a long-term, mutually monogamous relationship*
  - —persons seeking evaluation or treatment for a sexually transmitted disease
  - —men who have sex with men

*persons with more than one sex partner during the previous 6 months

Adults at Risk for HBV Infection

- Percutaneous or mucosal exposure to blood
  - —current or recent IDU
  - —household contacts of HBsAg-positive persons
  - —residents and staff of facilities for developmentally disabled persons
  - —healthcare and public safety workers with risk for exposure to blood or blood-contaminated body fluids
  - —persons with end-stage renal disease

Adults at Risk for HBV Infection

- Others groups
  - —international travelers to regions with high or intermediate levels (HBsAg prevalence of 2% or higher) of endemic HBV infection
  - —persons with HIV infection

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

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

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

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

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

Twinrix

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

Twinrix

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

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.

Serologic Testing of Vaccine Recipients

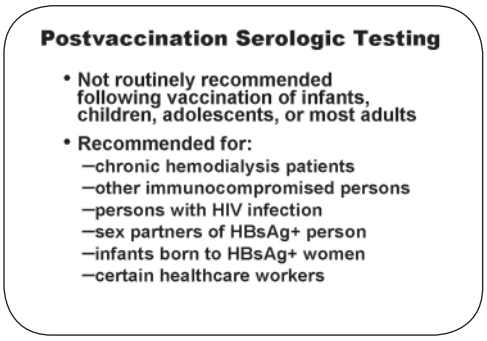
Prevaccination Serologic Testing

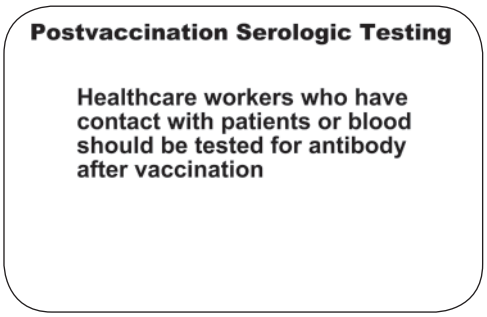
The decision to screen potential vaccine recipients for prior infection depends on the cost of vaccination, the cost of testing for susceptibility, and the expected prevalence of immune persons in the population being screened. Prevaccination testing is recommended for all foreign-born persons (including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

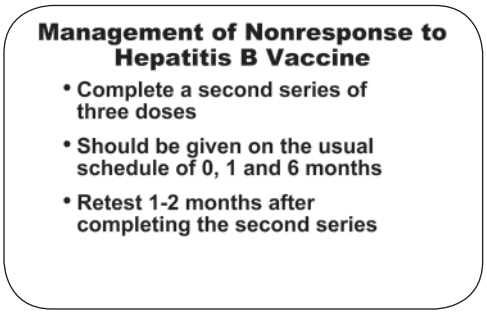
Prevaccination Serologic Testing

- Not indicated before routine vaccination of infants or children
- Recommended for
  - —all persons born in Africa, Asia, the Pacific Islands, and other regions with HBsAg prevalence of 8% or higher
  - —household, sex, and needle-sharing contacts of HBsAg-positive persons
  - —HIV-infected persons
- Consider for
  - —Groups with high risk of HBV infection (MSM, IDU, incarcerated persons)

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







Postvaccination Serologic Testing

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

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).

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.

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 probable parenteral exposure to HBsAg-positive blood (see postexposure prophylaxis table on page 232).

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

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, on the next page).

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.

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

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

response status of the exposed person. Recommended postexposure prophylaxis is described in the table below.

Recommended Postexposure Prophylaxis for Occupational Exposure to Hepatitis B Virus

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

* Persons who have previously been infected with HBV are immune to reinfection and do not require postexposure prophylaxis
** Hepatitis B surface antigen
† Hepatitis B immune globulin; dose is 0.06 mL/kg administered intramuscularly
§ A responder is a person with adequate levels of serum antibody to HBsAg (i.e., anti-HBs ≥10 mIU/mL)
‡ A nonresponder is a person with inadequate response to vaccination (i.e., serum anti-HBs <10 mIU/mL)
†† The option of giving one dose of HBIG and reinitiating the vaccine series is preferred for nonresponders who have not completed a second 3-dose vaccine series. For persons who previously completed a second vaccine series but failed to respond, two doses of HBIG are preferred.
¶ Antibody to HBsAg

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

Non-Occupational Exposure to an HBsAg-Positive Source

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

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

Non-Occupational Exposure to a Source with Unknown HBsAg Status

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

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 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

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

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.

Hepatitis B Vaccine Contraindications and Precautions

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

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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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.

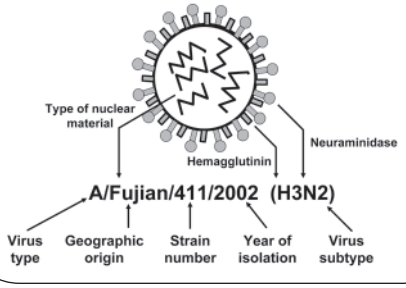
Influenza Virus

- 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.

Since the late 19th century, four occurrences of antigenic shifts have led to major pandemics (1889–1891, 1918–1920, 1957–1958, and 1968–1969). A pandemic starts from a single focus and spreads along routes of travel. Typically, there are

high attack rates involving all age groups, and mortality is usually markedly increased. Severity is 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.

Influenza Clinical Features

- Incubation period 2 days (range 1-4 days)
- Severity of illness depends on prior experience with related variants
- Abrupt onset of fever, myalgia, sore throat, nonproductive cough, headache

"Classic" influenza disease is characterized by the abrupt onset of fever, myalgia, sore throat, nonproductive cough, and headache. The fever is usually 101°–102°F, and accompanied by prostration. The onset of fever is often so abrupt that the exact hour is recalled by the patient. Myalgias mainly affect the back muscles. Cough is believed to be a result of tracheal epithelial destruction. Additional symptoms may include rhinorrhea (runny nose), headache, substernal chest burning and ocular symptoms (e.g., eye pain and sensitivity to light).

Systemic symptoms and fever usually last from 2 to 3 days, rarely more than 5 days. They may be decreased by such

medications as aspirin or acetaminophen. Aspirin should not be used for infants, children, or teenagers because they may be at risk for contracting Reye syndrome following an influenza infection. Recovery is usually rapid, but some patients may have lingering depression and asthenia (lack of strength or energy) for several weeks.

Complications

Influenza Complications

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

The most frequent complication of influenza is pneumonia, most commonly secondary bacterial pneumonia (e.g., *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Staphylococcus aureus*). Primary influenza viral pneumonia is an uncommon complication with a high fatality rate. Reye syndrome is a complication that occurs almost exclusively in children taking aspirin, primarily in association with influenza B (or varicella zoster), and presents with severe vomiting and confusion, which may progress to coma due to swelling of the brain.

Other complications include myocarditis (inflammation of the heart) and worsening of chronic bronchitis and other chronic pulmonary diseases. Death is reported in 0.5–1 per 1,000 cases. The majority of deaths occur among persons 65 years of age and older.

Impact of Influenza

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

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

- 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

The risk for complications and hospitalizations from influenza are higher among persons 65 years of age and older, young children, and persons of any age with certain underlying medical conditions. An average of more than 200,000 hospitalizations per year are related to influenza, more than 57% of which are among persons younger than 65 years. A greater number of hospitalizations occur during years that influenza A (H3N2) is predominant. In nursing homes, attack rates may be as high as 60%, with fatality rates as

high as 30%. The cost of a severe epidemic has been estimated to be $12 billion.

Among children 0–4 years of age, hospitalization rates have varied from 100 per 100,000 healthy children to as high as 500 per 100,000 for children with underlying medical conditions. Hospitalization rates for children 24 months of age and younger are comparable to rates for persons 65 and older. Children 24-59 months of age are at less risk of hospitalization from influenza than are younger children, but are at increased risk for influenza-associated clinic and emergency department visits.

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

An influenza pandemic could affect up to 200 million people and result in up to 400,000 deaths. The 1918–1919 influenza pandemic is believed to have resulted in the death of at least 500,000 Americans in less than a year. Planning for pandemic influenza is a critical component of public health preparedness activities and should be conducted by all local and state public health agencies. The federal pandemic plan is available on the Department of Health and Human Services website at http://www.hhs.gov/pandemicflu/plan/

Laboratory Diagnosis

The diagnosis of influenza is usually suspected on the basis of characteristic clinical findings, particularly if influenza has been reported in the community.

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.

Influenza Epidemiology

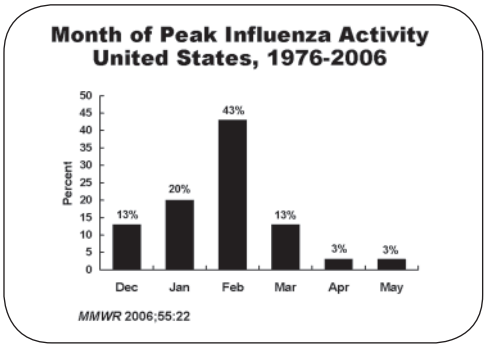
• Reservoir	Human, animals (type A only)
• Transmission	Respiratory Probably airborne
• Temporal pattern	Peak December – March in temperate climate May occur earlier or later
• Communicability	1 day before to 5 days after onset (adults)

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 1976–2006, peak influenza activity in the United States occurred most frequently in January (20% of seasons) and February (43% of seasons). However, peak influenza activity occurred in March, April, or May in 19% of seasons. Influenza occurs throughout the year in tropical areas.

Communicability

Adults can transmit influenza from the day before symptom onset to approximately 5 days after symptoms begin. Children can transmit influenza to others for 10 or more days.

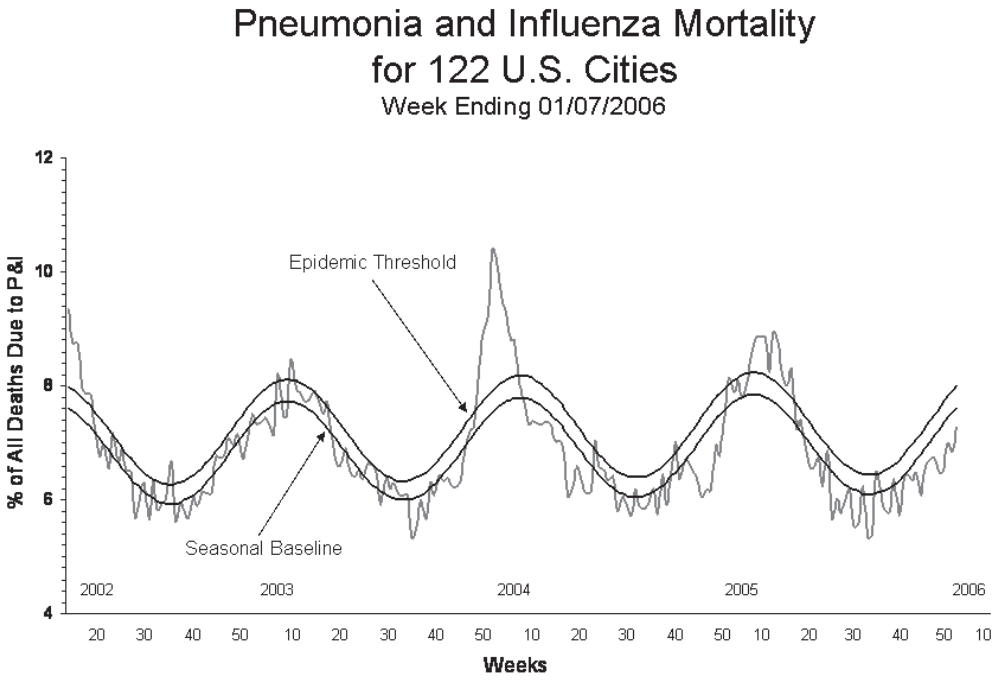
Secular Trends in the United States

There is a documented association between influenza and increased morbidity in high-risk adult populations. Hospitalization for adults with high-risk medical conditions increases two- to fivefold during major epidemics.

The impact of influenza in the United States is quantified by measuring pneumonia and influenza (P and I) deaths.

Death certificate data are collected from 122 U.S. cities with populations of more than 100,000 (total of approximately 70,000,000). P and I deaths include all deaths for which pneumonia is listed as a primary or underlying cause or for which influenza is listed on the death certificate.

An expected ratio of deaths due to P and I compared with all deaths for a given period of time is determined. The epidemic threshold for influenza seasons is generally estimated at 1.645 standard deviations above observed P and I deaths for the previous 5-year period excluding periods during influenza outbreaks. Influenza epidemic activity is signaled when the ratio of deaths due to P and I exceeds the threshold ratio for 2 consecutive weeks.



Influenza Vaccine

Characteristics

Two types of influenza vaccine are available in the United States. Trivalent inactivated influenza vaccine (TIV) has been available since the 1940s. TIV is administered by the intramuscular route and currently contains three inactivated viruses: type A (H1N1), type A (H3N2), and type B. Only split-virus and subunit inactivated vaccines are available in the United States. Vaccine viruses are grown in chicken eggs, and the final product contains residual egg protein. The vaccine is available in both pediatric (0.25-mL dose) and adult (0.5-mL dose) formulations. TIV is available with thimerosal as a preservative (in multidose vials), and in reduced and preservative free formulations.

Influenza Vaccines

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

For the 2006–2007 influenza season four manufacturers provided TIV. Fluzone (sanofi pasteur) was available in multidose vials, in a thimerosal-free pediatric formulation (0.25 mL) in single-dose syringes, and in a thimerosal-free adult formulation in single-dose syringes and vials. Fluzone was the only TIV approved for use among children younger than 48 months during the 2006–2007 season. Fluvirin (Novartis) was available in multidose vials. Fluvirin is approved only for persons 4 years of age and older. Fluarix (GlaxoSmithKline) was available in a reduced-thimerosal ("preservative free") single-dose syringe for persons 18 years of age and older. FluLaval (GlaxoSmithKline) was available in a multidose vial (with thimerosal as a preservative) for persons 18 years of age and older.

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.

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.

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.

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

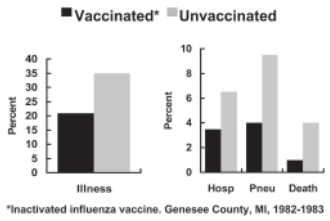
Inactivated Influenza Vaccine Efficacy

- 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

similar to the circulating strain. However, the vaccine is only 30%–40% effective in preventing illness among persons 65 years of age and older.

Although the vaccine is not highly effective in preventing clinical illness among the elderly, it is effective in preventing complications and death. Among elderly persons, the vaccine is 50%–60% effective in preventing hospitalization and 80% effective in preventing death. During a 1982–1983 influenza outbreak in Genesee County, Michigan, unvaccinated nursing home residents were four times more likely to die than were vaccinated residents.

Influenza and Complications Among Nursing Home Residents



*Inactivated influenza vaccine. Genesee County, MI, 1982-1983

LAIV

LAIV has been tested in groups of both healthy children and healthy adults. A randomized, double-blind, placebo-controlled trial among healthy children 60–84 months of age assessed the efficacy of the trivalent LAIV against culture-confirmed influenza during two influenza seasons. In year 1, when vaccine and circulating virus strains were well matched, efficacy was 87% against culture-confirmed influenza. In year 2, when the type A component was not well matched between vaccine and circulating virus strains, efficacy was also 87%. Other results from this trial included a 27% reduction in febrile otitis media and a 28% reduction in otitis media with concomitant antibiotic use. Receipt of LAIV also resulted in decreased fever and otitis media in vaccine recipients who developed influenza.

LAIV Efficacy in Healthy Children

- 87% effective against culture-confirmed influenza in children 5-7 years old
- 27% reduction in febrile otitis media (OM)
- 28% reduction in OM with accompanying antibiotic use
- Decreased fever and OM in vaccine recipients who developed influenza

A randomized, double-blind, placebo-controlled trial among 3,920 healthy working adults aged 18–49 years assessed several endpoints and documented reductions in illness, absenteeism, healthcare visits, and medication use during influenza outbreak periods. This study was conducted during the 1997–98 influenza season, when the vaccine and circulating type A strains were not well matched. This study did not include laboratory virus testing of cases. 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 patient visits. The optimal time for vaccination efforts is usually during October and November. In October vaccination in provider-based settings should start or continue for all patients,-both high risk and healthy-and extend through November. Vaccination of children aged 6 months through

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

8 years of age who are receiving vaccine for the first time should also begin in October, if not done earlier, because those children need a second dose 4 to 6 weeks after the initial dose, depending upon whether they are receiving inactivated influenza vaccine or LAIV. Organized vaccination campaigns should be scheduled no earlier than mid-October. Vaccine may be given up to and even after influenza activity is documented in a region. Although most influenza vaccination activities should be completed by December (particularly for high-risk groups), providers should continue to provide vaccine throughout influenza season.

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.

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

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).

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

Persons 6 months of age and older with a chronic illness should receive TIV annually. These chronic illnesses include the following:

- pulmonary illnesses, such as emphysema, chronic bronchitis, or asthma
- cardiovascular illnesses, such as congestive heart failure
- metabolic diseases, including diabetes mellitus
- renal dysfunction
- hemoglobinopathy, such as sickle cell disease
- immunosuppression, including human immunodeficiency virus (HIV) infection
- any condition (e.g., cognitive dysfunction, spinal cord injury, seizure disorder, or other neuromuscular disorder) that can compromise respiratory function or the handling of respiratory secretions

Case reports and limited studies suggest that pregnant women may be at increased risk for serious medical complications of influenza as a result of increases in heart rate, stroke volume and oxygen consumption; decreases in lung capacity; and changes in immunologic function. A 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.

Pregnancy and Inactivated Influenza Vaccine

- Risk of hospitalization 4 times higher than nonpregnant women
- Risk of complications comparable to nonpregnant women with high-risk medical conditions
- Vaccination (with TIV) recommended if pregnant during influenza season
- Vaccination can occur during any trimester

ACIP recommends vaccination of women who will be pregnant during influenza season. Vaccination can occur during any trimester. Influenza season in the United States generally occurs in December through March. Only TIV should be administered to pregnant women.

Available data suggest that persons with HIV infection may have prolonged influenza illnesses and are at increased risk of complications of influenza. Many persons with HIV infection will develop protective antibody titers following inactivated influenza vaccine. In persons who have advanced HIV disease and low CD4+ T-lymphocyte cell counts, TIV vaccine may not induce protective antibody titers. A second dose of vaccine does not improve the immune response in these persons.

HIV Infection and Inactivated Influenza Vaccine

- Persons with HIV at increased risk of complications of influenza
- TIV induces protective antibody titers in many HIV infected persons
- Transient increase in HIV replication reported
- TIV will benefit many HIV-infected persons

Some studies have demonstrated a transient increase in viral titer in the blood of vaccinated persons infected with HIV. There is no evidence of deterioration in CD4 counts or progression of clinical HIV disease. Because influenza can result in serious illness and complications and because influenza vaccination may result in protective antibody titers, ACIP believes that influenza vaccination will benefit many persons with HIV infection. LAIV should not be administered to persons with HIV infection.

Persons who have contact with high-risk persons should receive TIV. These include healthcare 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

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 6-59 months at increased risk of hospitalization and physician visits
- Inactivated influenza vaccination of healthy children 6-59 months is recommended
- Vaccination of household contacts and other caregivers of children younger than 59 months 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

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 2005, the ACIP recommended that healthy children aged 6–59 months be vaccinated because of the increased risk of influenza-related hospitalization and physician visits in this age group. Household contacts and other caregivers of children younger than 59 months of age are also encouraged to receive annual influenza vaccination.

LAIV

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 at least 6 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.

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

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

Inactivated Influenza Vaccine Adverse Reactions

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

severe egg allergy. Persons who have developed hives, had swelling of the lips or tongue, or have experienced acute respiratory distress or collapse after eating eggs should consult a physician for appropriate evaluation to assist in determining whether influenza vaccination may proceed or should be deferred. Persons with documented immunoglobulin E (IgE)-mediated hypersensitivity to eggs—including those who have had occupational asthma or other allergic responses from exposure to egg protein—may also be at increased risk for reactions from influenza vaccines, and similar consultation should be considered. Protocols have been published for influenza vaccination of patients who have egg allergies and medical conditions that place them at increased risk for influenza infection or its complications.

The potential exists for hypersensitivity reactions to any vaccine component. Although exposure to vaccines containing thimerosal can lead to induction of hypersensitivity, most patients do not develop reactions to thimerosal administered as a component of vaccines, even when patch or intradermal tests for thimerosal indicate hypersensitivity. When it has been reported, hypersensitivity to thimerosal has usually consisted of local delayed-type hypersensitivity reactions.

Unlike the 1976 swine influenza vaccine, subsequent inactivated vaccines prepared from other virus strains have not been clearly associated with an increased frequency of Guillain-Barré syndrome (GBS). However, obtaining a precise estimate of a small increase in risk is difficult for a rare condition such as GBS, which has an annual background incidence of only one to two cases per 100,000 adult population. Among persons who received the swine influenza vaccine in 1976, the rate of GBS exceeded the background rate by less than one case per 100,000 vaccinations. Even if GBS were a true adverse reaction in subsequent years, the estimated risk for GBS was much lower than one per 100,000. Further, the risk is substantially less than that for severe influenza or its complications, which could be prevented by vaccination, especially for persons aged 65 years or older and those with a medical indication for influenza vaccine.

Although the incidence of GBS in the general population is very low, persons with a history of GBS have a substantially greater likelihood of subsequently developing GBS than do persons without such a history, irrespective of vaccination. As a result, the likelihood of coincidentally developing GBS after influenza vaccination is expected to be greater among persons with a history of GBS than among persons with no history of GBS. Whether influenza vaccination might be causally associated with this risk for recurrence is not known. It seems prudent for persons known to have developed GBS

within 6 weeks of a previous influenza vaccination to avoid subsequent influenza vaccination. For most persons with a history of GBS who are at high risk for severe complications from influenza, the established benefits of influenza vaccination justify yearly vaccination.

LAIV

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 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.

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

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

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

(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.

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 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

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 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.

Influenza Vaccine Strategies to Improve Coverage

- Ensure systematic and automatic offering of TIV to high-risk groups
- Educate healthcare providers and patients
- Address concerns about adverse events
- Emphasize physician recommendation

In physicians' offices and outpatient clinics, persons who should receive inactivated influenza vaccine should be identified and their charts marked. TIV use should be promoted, encouraged and recommended beginning in October and continuing through the influenza season. Those without regularly scheduled visits should receive reminders.

In nursing homes and other residential long-term care facilities, immunization with TIV should be routinely provided to all residents at one period of time immediately preceding the influenza season; consent should be obtained at the time of admission.

In acute care hospitals and continuing care centers, persons for whom vaccine is recommended who are hospitalized from October through March should be vaccinated prior to discharge. In outpatient facilities providing continuing care to high-risk patients (e.g., hemodialysis centers, hospital specialty-care clinics, outpatient rehabilitation programs), all patients should be offered TIV shortly before the onset of the influenza season.

Visiting nurses and others providing home care to high-risk persons should identify high-risk patients and administer TIV in the home, if necessary.

In facilities providing services to persons 50 years of age and older (e.g., retirement communities, recreation centers), inactivated influenza vaccine should be offered to all unvaccinated residents or attendees on site. Education and publicity programs should also be conducted in conjunction with other interventions.

For travelers, indications for influenza vaccine should be reviewed prior to travel and vaccine offered, if appropriate.

Administrators of all of the above facilities and organizations should arrange for influenza vaccine to be offered to all personnel before the influenza season. Additionally, household members of high-risk persons and others with whom they will be in contact should receive written information about why they should receive the vaccine and where to obtain it.

Influenza Antiviral Agents*

- Amantadine and rimantadine
  - —Not recommended because of documented resistance in U.S. influenza isolates
- 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

Antiviral Agents for Influenza

In the United States, four antiviral agents are approved for preventing or treating influenza: amantadine, rimantadine, zanamivir, and oseltamivir.

Testing of influenza A isolates from the United States and Canada has demonstrated that many of these viruses are resistant to amantadine and rimantadine. The ACIP recommends that neither amantadine nor rimantadine be used for

the treatment or chemoprophylaxis of influenza A in the United States until susceptibility to these antiviral drugs has been re-established.

Zanamivir and oseltamivir are members of a new class of drugs called neuraminidase inhibitors and are active against both influenza type A and type B. Zanamivir is provided as a dry powder that is administered by inhalation. It is approved for treatment of uncomplicated acute influenza A or B in persons 7 years of age and older who have been symptomatic for no more than 48 hours. Oseltamivir is provided as an oral capsule. It is approved for the treatment of uncomplicated influenza A or B in persons 1 year of age and older who have been symptomatic for no more than 48 hours. Zanamivir is approved for prophylaxis of influenza in persons 5 years and older. Oseltamivir is approved for prophylaxis of influenza infection among persons 1 year of age and older.

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.

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

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

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

CDC receives weekly surveillance reports from the states showing the extent of influenza activity. Reports are classified into four categories: no cases, sporadic, regional (cases occurring in counties collectively contributing less than 50% of a state's population), widespread (cases occurring in counties collectively contributing 50% or more of a state's population).

Weekly surveillance reports are available at http://www.cdc.gov/flu/weekly/fluactivity.htm

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Influenza

16

Pneumococcal Disease

Streptococcus pneumoniae causes an acute bacterial infection. The bacterium, also called pneumococcus, was first isolated by Pasteur in 1881 from the saliva of a patient with rabies. The association between the pneumococcus bacterium and lobar pneumonia was first described by Friedlander and Talamon in 1883, but pneumococcal pneumonia was confused with other types of pneumonia until the discovery of the Gram stain in 1884. From 1915 to 1945, the chemical structure and antigenicity of the pneumococcal capsular polysaccharide, its association with virulence, and the role of bacterial polysaccharides in human disease were explained. More than 80 serotypes of pneumococci had been described by 1940.

Efforts to develop effective pneumococcal vaccines began as early as 1911. However, with the advent of penicillin in the 1940s, interest in the vaccine declined, until it was observed that many patients still died despite antibiotic treatment. By the late 1960s, efforts were again being made to develop a polyvalent pneumococcal vaccine. The first pneumococcal vaccine was licensed in the United States in 1977. The first conjugate pneumococcal vaccine was licensed in 2000.

Pneumococcal Disease

- *S. pneumoniae* first isolated by Pasteur in 1881
- Confused with other causes of pneumonia until discovery of Gram stain in 1884
- More than 80 serotypes described by 1940
- First U.S. vaccine in 1977

Streptococcus pneumoniae

Streptococcus pneumoniae bacteria are lancet-shaped, gram-positive, facultative anaerobic organisms. They are typically observed in pairs (diplococci) but may also occur singularly or in short chains. Some pneumococci are encapsulated, their surfaces composed of complex polysaccharides. Encapsulated organisms are pathogenic for humans and experimental animals, whereas organisms without capsular polysaccharides are not. Capsular polysaccharides are the primary basis for the pathogenicity of the organism. They are antigenic and form the basis for classifying pneumococci by serotypes. Ninety serotypes have been identified, based on their reaction with type-specific antisera. Type-specific antibody to capsular polysaccharide is protective. These antibodies and complement interact to opsonize pneumococci, which facilitates phagocytosis and clearance of the organism. Antibodies to some pneumococcal capsular polysaccharides may cross-react with related types as well as with other bacteria, providing protection against additional serotypes.

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

Streptococcus pneumoniae

- Gram-positive bacteria
- 90 known serotypes
- Polysaccharide capsule important virulence factor
- Type-specific antibody is protective

cerebrospinal fluid (CSF) of children younger than 6 years of age account for 80% of infections. These seven serotypes account for only about 50% of isolates from older children and adults.

Pneumococci are common inhabitants of the respiratory tract and may be isolated from the nasopharynx of 5% to 70% of healthy adults. Rates of asymptomatic carriage vary with age, environment, and the presence of upper respiratory infections. Only 5%–10% of adults without children are carriers. In schools and orphanages, 27%–58% of students and residents may be carriers. On military installations, as many as 50%–60% of service personnel may be carriers. The duration of carriage varies and is generally longer in children than adults. In addition, the relationship of carriage to the development of natural immunity is poorly understood.

Clinical Features

The major clinical syndromes of pneumococcal disease are pneumonia, bacteremia, and meningitis. The immunologic mechanism that allows disease to occur in a carrier is not clearly understood. However, disease most often occurs when a predisposing condition exists, particularly pulmonary disease.

Pneumococcal Pneumonia Clinical Features

- Abrupt onset
- Fever
- Shaking chills
- Pleuritic chest pain
- Productive cough
- Dyspnea, tachypnea, hypoxia

Pneumococcal pneumonia is the most common clinical presentation of pneumococcal disease among adults, although pneumonia alone is not considered to be "invasive" disease. The incubation period of pneumococcal pneumonia is short, about 1 to 3 days. Symptoms generally include an abrupt onset of fever and chills or rigors. Typically there is a single rigor, and repeated shaking chills are uncommon. Other common symptoms include pleuritic chest pain, cough productive of mucopurulent, rusty sputum, dyspnea (shortness of breath), tachypnea (rapid breathing), hypoxia (poor oxygenation), tachycardia (rapid heart rate), malaise, and weakness. Nausea, vomiting, and headaches occur less frequently.

Pneumococcal Pneumonia

- Estimated 175,000 hospitalizations per year in the United States
- Up to 36% of adult community-acquired pneumonia and 50% of hospital-acquired pneumonia
- Common bacterial complication of influenza and measles
- Case-fatality rate 5%-7%, higher in elderly

As many as 175,000 hospitalizations from pneumococcal pneumonia are estimated to occur annually in the United States. Pneumococci account for up to 36% of adult community-acquired pneumonia and 50% of hospital-acquired pneumonia. Pneumonia is a common bacterial complication of influenza and measles. The case-fatality rate is 5%–7% and may be much higher among elderly persons. Complications of pneumococcal pneumonia include empyema (i.e., infection of the pleural space), pericarditis (inflammation of the sac surrounding the heart), and endobronchial obstruction, with atelectasis and lung abscess formation.

Pneumococcal Bacteremia

- More than 50,000 cases per year in the United States
- Rates higher among elderly and very young infants
- Case-fatality rate ~20%; up to 60% among the elderly

More than 50,000 cases of pneumococcal bacteremia occur each year. Bacteremia occurs in about 25%–30% of patients with pneumococcal pneumonia. The overall case-fatality

rate for bacteremia is about 20% but may be as high as 60% among elderly patients. Patients with asplenia who develop bacteremia may experience a fulminant clinical course.

Pneumococci cause 13%–19% of all cases of bacterial meningitis in the United States. An estimated 3,000 to 6,000 cases of pneumococcal meningitis occur each year. One-fourth of patients with pneumococcal meningitis also have pneumonia. The clinical symptoms, CSF profile and neurologic complications are similar to other forms of purulent bacterial meningitis. Symptoms may include headache, lethargy, vomiting, irritability, fever, nuchal rigidity, cranial nerve signs, seizures and coma. The case-fatality rate of pneumococcal meningitis is about 30% but may be as high as 80% among elderly persons. Neurologic sequelae are common among survivors. Persons with a cochlear implant appear to be at increased risk of pneumococcal meningitis.

Pneumococcal Meningitis

- Estimated 3,000 - 6,000 cases per year in the United States
- Case-fatality rate ~30%, up to 80% in the elderly
- Neurologic sequelae common among survivors
- Increased risk after cochlear implant

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
- Cochlear implant

Children with functional or anatomic asplenia, particularly those with sickle cell disease, and children with human immunodeficiency virus (HIV) infection are at very high risk for invasive disease, with rates in some studies more than 50 times higher than those among children of the same age without these conditions (i.e., incidence rates of 5,000–9,000 per 100,000 population). Rates are also increased among children of certain racial and ethnic groups, in particular those of Alaska Native, African American, and certain American Indian groups (Arizona, New Mexico, and Navajo populations in Colorado and Utah). The reason for this increased risk by race and ethnicity is not known with certainty but was also noted for invasive *Haemophilus influenzae* infection (also an encapsulated bacterium). Attendance at a child care center has also been shown to increase the risk of invasive pneumococcal disease and acute otitis media 2–3-fold among children younger than 59 months of age. Children with a cochlear implant are at increased risk for pneumococcal meningitis.

Laboratory Diagnosis

A definitive diagnosis of infection with *S. pneumoniae* generally relies on isolation of the organism from blood or other normally sterile body sites. Tests are also available to detect capsular polysaccharide antigen in body fluids.

The appearance of lancet-shaped diplococci on Gram stain is suggestive of pneumococcal infection, but interpretation of stained sputum specimens may be difficult because of the presence of normal nasopharyngeal bacteria. The suggested criteria for obtaining a diagnosis of pneumococcal pneumonia using Gram stained sputnum includes more than 25 white blood cells and fewer than 10 epithelial cells per 100-power field, and a predominance of gram-positive diplococci.

The quellung reaction (capsular swelling; capsular precipitation reaction) is a test that provides rapid identification of pneumococci in clinical specimens, including spinal fluid, sputum, and exudates. The procedure involves mixing loopfuls of bacteria in suspension, pneumococcal antiserum, and methylene blue on the surface of a glass slide and examining under oil immersion. If the reaction is positive, the organism will be surrounded by a large capsule.

Several rapid tests for detection of pneumococcal polysaccharide antigen in CSF and other body fluids are available. These tests generally lack sufficient sensitivity or specificity to assist in the diagnosis of invasive pneumococcal disease.

Medical Management

Resistance to penicillin and other antibiotics is common. In some areas of the United States, up to 40% of invasive

pneumococcal isolates are resistant to penicillin. Treatment will usually include a broad-spectrum cephalosporin, and often vancomycin, until results of antibiotic sensitivity testing are available.

Epidemiology

Occurrence

Pneumococcal disease occurs throughout the world.

Reservoir

S. pneumoniae is a human pathogen. The reservoir for pneumococci is presumably the nasopharynx of asymptomatic human carriers. There is no animal or insect vector.

Transmission

Transmission of *S. pneumoniae* occurs as the result of direct person-to-person contact via respiratory droplets and by autoinoculation in persons carrying the bacteria in their upper respiratory tract. The pneumococcal serotypes most often responsible for causing infection are those most frequently found in carriers. The spread of the organism within a family or household is influenced by such factors as crowding, season, and the presence of upper respiratory infections or pneumococcal disease such as pneumonia or otitis media. The spread of pneumococcal disease is usually associated with increased carriage rates. However, high carriage rates do not appear to increase the risk of disease transmission in households.

Temporal Pattern

Pneumococcal infections are more common during the winter and in early spring when respiratory diseases are more prevalent.

Communicability

The period of communicability for pneumococcal disease is unknown, but presumably transmission can occur as long as the organism appears in respiratory secretions.

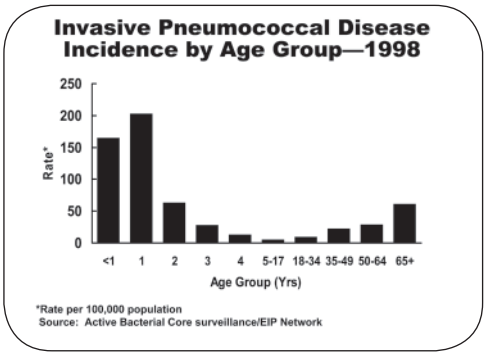
Pneumococcal Disease Epidemiology

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

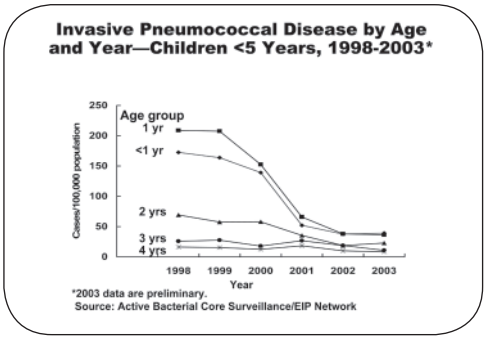
Secular Trends in the United States

Estimates of the incidence of pneumococcal disease have been made from a variety of population-based studies. More than 40,000 cases and more than 4,400 deaths from invasive pneumococcal disease (bacteremia and meningitis) are estimated to have occurred in the United States in 2005.

More than half of these cases occurred in adults who had an indication for pneumococcal polysaccharide vaccine. In addition, there are thousands of cases of nonbacteremic pneumonia, and millions of cases of otitis media, which are considered noninvasive infections.



The overall incidence of invasive pneumococcal disease (bacteremia, meningitis, or other infection of a normally sterile site) in the United States in 1998–1999 was estimated to be approximately 24 cases per 100,000 population. However, incidence rates vary greatly by age group. The highest rates of invasive pneumococcal disease occur among young children, especially those younger than 2 years of age. In 1998, the rate of invasive disease in this age group was estimated to be 188 per 100,000 population; this age group accounted for 20% of all cases of invasive pneumococcal disease. Incidence was lowest among persons 5–17 years of age, and increased to 61 per 100,000 population among persons 65 years of age and older.



Data from the Active Bacterial Core surveillance (ABCs) system suggest that the use of pneumococcal conjugate vaccine is having an impact on the incidence of invasive disease among young children. Data from 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

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

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 (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 Polysaccharide Vaccine

- Purified capsular polysaccharide antigen from 23 types of pneumococcus
- Account for 88% of bacteremic pneumococcal disease
- Cross-react with types causing additional 8% of disease

Pneumococcal Conjugate Vaccine

The first pneumococcal conjugate vaccine (PCV7) was licensed in the United States in 2000. It includes purified capsular polysaccharide of seven serotypes of *S. pneumoniae* (4, 9V, 14, 19F, 23F, 18C, and 6B) conjugated to a nontoxic variant of diphtheria toxin known as CRM197. The serotypes included in PCV7 accounted for 86% of bacteremia, 83% of meningitis, and 65% of acute otitis media among children younger than 6 years of age in the United States during 1978–1994. Additional pneumococcal polysaccharide conjugate vaccines containing 9 and 11 serotypes of *S. pneumoniae* are being developed. The vaccine is administered intramuscularly. It does not contain thimerosal as a preservative, and is available only in single-dose vials.

Pneumococcal Conjugate Vaccine

- Pneumococcal polysaccharide conjugated to nontoxic diphtheria toxin (7 serotypes)
- Vaccine serotypes account for 86% of bacteremia and 83% of meningitis among children <6 years of age

Immunogenicity and Vaccine Efficacy

Pneumococcal Polysaccharide Vaccine

More than 80% of healthy adults who receive 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.

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

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 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

Pneumococcal Conjugate Vaccine

- Highly immunogenic in infants and young children, including those with high-risk medical conditions
- >90% effective against invasive disease
- Less effective against pneumonia and acute otitis media

After four doses of PCV7 vaccine, more than 90% of healthy infants develop antibody to all seven serotypes contained in the vaccine. PCV7 has been shown to be immunogenic in infants and children, including those with sickle cell disease and HIV infection. In a large clinical trial, PCV7 was shown to reduce invasive disease caused by vaccine serotypes by 97%, and reduce invasive disease caused by all serotypes, including serotypes not in the vaccine, by 89%. Efficacy against pneumonia varied depending on the specificity of the diagnosis. The vaccine reduced clinically diagnosed pneumonia by 11%, but reduced pneumonia confirmed by x-ray with consolidation of 2.5 or more centimeters by 73%. Children who received PCV7 had 7% fewer episodes of acute otitis media and underwent 20% fewer tympanostomy tube placements than did unvaccinated children. The duration of protection following PCV7 is currently not known. There is evidence that PCV7 reduces nasopharyngeal carriage of pneumococcal serotypes included in the vaccine.

Vaccination Schedule and Use

Pneumococcal Polysaccharide Vaccine Recommendations

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

Pneumococcal Polysaccharide Vaccine

Pneumococcal polysaccharide vaccine should be administered routinely to all adults 65 years of age and older. The vaccine is also indicated for persons 2 years of age and older with a normal immune system who have a chronic illness, including cardiovascular disease, pulmonary disease, diabetes, alcoholism, cirrhosis, cerebrospinal fluid leak, or a cochlear implant.

Immunocompromised persons 2 years of age and older who are at increased risk of pneumococcal disease or its complications should also be vaccinated. This group includes persons with splenic dysfunction or absence (either from disease or surgical removal), Hodgkin disease, lymphoma, multiple myeloma, chronic renal failure, nephrotic syndrome (a type of

kidney disease), or conditions such as organ transplantation associated with immunosuppression. Persons immunosuppressed from chemotherapy or high-dose corticosteroid therapy (14 days or longer) should be vaccinated. Persons 2 years of age and older with asymptomatic or symptomatic HIV infection should be vaccinated. Pneumococcal vaccine should be considered for persons living in special environments or social settings with an identified increased risk of pneumococcal disease or its complications, such as certain Native American (i.e., Alaska Native, Navajo, and Apache) populations.

If elective splenectomy or cochlear implant is being considered, the vaccine should be given at least 2 weeks before the procedure. If vaccination prior to the procedure is not feasible, the vaccine should be given as soon as possible after surgery. Similarly, there should also be a 2-week interval between vaccination and initiation of cancer chemotherapy or other immunosuppressive therapy, if possible.

Providers should not withhold vaccination in the absence of an immunization record or complete record. The patient's verbal history may be used to determine vaccination status. Persons with uncertain or unknown vaccination status should be vaccinated.

The target groups for pneumococcal polysaccharide vaccine and influenza vaccine overlap. These vaccines should be given at the same time at different sites if indicated, although most recipients need only a single lifetime dose of PPV23 (see Revaccination).

Pneumococcal Conjugate Vaccine

All children younger than 24 months of age and children age 24–59 months with a high-risk medical condition should be routinely vaccinated with PCV7. The primary series beginning in infancy consists of three doses routinely given at 2, 4, and 6 months of age. A fourth (booster) dose is recommended at 12–15 months of age. PCV7 should be administered at the same time as other routine childhood immunizations, using a separate syringe and injection site. For children vaccinated at younger than 12 months of age, the minimum interval between doses is 4 weeks. Doses given at 12 months of age and older should be separated by at least 8 weeks.

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

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 children aged 12–23 months should receive two doses of vaccine, at least 8 weeks apart. Previously unvaccinated healthy children 24–59 months of age should receive a single dose of PCV7. Unvaccinated children 24–59 months of age with sickle cell disease, asplenia, HIV infection, chronic illness, cochlear implant, or immunocompromising conditions should receive two doses of PCV7 separated by at least 8 weeks.

PCV7 is not routinely recommended for persons older than 59 months of age.

Few data are available on the use of PCV7 among children previously vaccinated with 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, cochlear implant, 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.

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

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 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 consideredto 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.

Contraindications and Precautions to Vaccination

Pneumococcal Vaccines
Contraindications and Precautions

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

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.

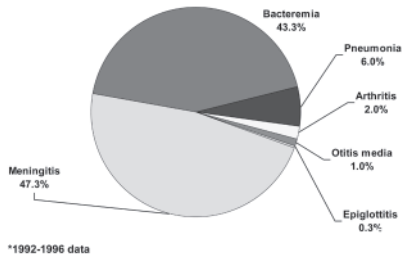
Meningococcal Disease Pathogenesis

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

Pathogenesis

Meningococci are transmitted by droplet aerosol or secretions from the nasopharynx of colonized persons. The bacteria attach to and multiply on the mucosal cells of the nasopharynx. In a small proportion (less than 1%) of colonized persons, the organism penetrates the mucosal cells and enters the bloodstream. The bacteria spread by way of the blood to many organs. In about 50% of bacteremic persons, the organism crosses the blood–brain barrier into the cerebrospinal fluid and causes purulent meningitis. An antecedent upper respiratory infection may be a contributing factor.

Neisseria meningitidis* Clinical Manifestations



*1992-1996 data

Meningococcal Meningitis

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

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.

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.

Meningococcemia

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

Less common presentations of meningococcal disease include pneumonia (5%–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.

Risk factors for the development of meningococcal disease include deficiencies in the terminal common complement pathway and functional or anatomic asplenia. Persons with HIV infection are probably at increased risk for meningococcal disease. Certain genetic factors (such as polymorphisms in the genes for mannose-binding lectin and tumor necrosis factor) may also be risk factors.

Family members of an infected person are at increased risk for meningococcal disease. Antecedent upper respiratory tract infection, household crowding, and both active and passive smoking also are also associated with increased risk. In the United States, African Americans and persons of low socioeconomic status have been consistently at higher risk; however, race and low socioeconomic status are likely markers for differences in factors such as household crowding rather than risk factors. During outbreaks, bar or nightclub patronage and alcohol use have also been associated with higher risk for disease.

Cases of invasive meningococcal disease, including at least two fatal cases, have been reported among microbiologists. These persons have worked with *N. meningitidis* isolates rather than patient specimens.

Studies have shown that college freshmen living in dormitories are at modestly increased risk of meningococcal disease. However, U.S. college students are not at higher risk for meningococcal disease than other persons of similar age.

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

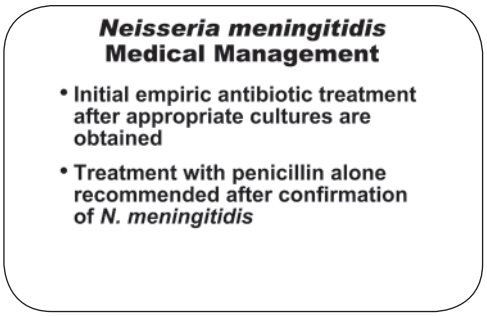
Invasive meningococcal disease is typically diagnosed by isolation of *N. meningitidis* from a normally sterile site. However, sensitivity of bacterial culture may be low, particularly when performed after initiation of antibiotic therapy. A Gram stain of cerebrospinal fluid showing gram-negative diplococci 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

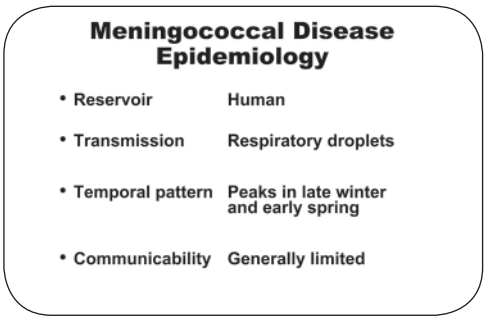
- Bacterial culture
- Gram stain
- Non-culture methods
  - —antigen detection in CSF
  - —serology



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.

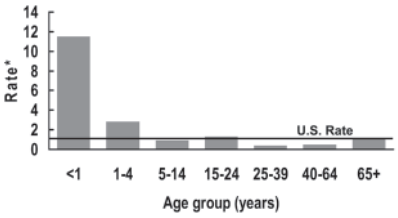
In the United States, meningococcal outbreaks account for less than 5% of reported cases (95%–97% of cases are sporadic). However, since 1991, the frequency of localized outbreaks has increased. Most of these outbreaks have been caused by serogroup C. Since 1997, localized outbreaks caused by serogroups 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.

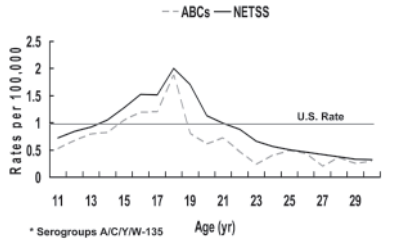
Meningococcal Disease—United States, 1972-2004



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 Vaccines

Characteristics

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 Polysaccharide Vaccine (MPSV)

The first meningococcal polysaccharide vaccine was licensed in the United States in 1974. The current quadrivalent A, C, Y, W-135 polysaccharide vaccine (Menomune, sanofi pasteur) was licensed in 1978. Each dose consists of 50 mcg of each of the four purified bacterial capsular polysaccharides. The vaccine contains lactose as a stabilizer.

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)

- Menactra® (sanofi pasteur)
- Quadrivalent polysaccharide vaccine (A, C, Y, W-135) conjugated to diphtheria toxoid
- Administered by intramuscular injection
- Single-dose vials do not contain a preservative

Meningococcal Conjugate Vaccine (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, little boost in antibody titer occurs with repeated doses; the antibody which is produced is relatively low-affinity IgM, and "switching" from IgM to IgG production is poor.

A protective level of antibody is usually achieved within 7–10 days of vaccination. Among infants and children younger than 5 years of age, the level of antibody against serogroup A and C polysaccharide decreases substantially during the first 3 years following a single dose of vaccine. In healthy adults, antibody levels also decrease, but antibodies are detectable as long as 10 years after vaccination. Although vaccine-induced protection likely persists in school-aged children and adults for at least 3 years, the efficacy of the group A vaccine in children younger than 5 years of age may decrease markedly within this period. In one study, efficacy declined from more than 90% to less than 10% 3 years after vaccination among children who were younger than 4 years of age when vaccinated. Efficacy was 67% among children who were older than 4 years of age at vaccination.

Meningococcal Conjugate Vaccine

The approval of MCV was based on studies that compared the serologic response to a single dose to the response of persons of similar age who received a single dose of meningococcal polysaccharide vaccine. In these studies a similar proportion of recipients achieved at least a fourfold rise in serum bactericidal antibody titer assay following 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 conjugate vaccines. Pure polysaccharide vaccines have little or no effect on carriage of the vaccine organism.

Vaccination Schedule And Use

Meningococcal Polysaccharide Vaccine

For children 2 years of age and older and adults, 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 who live in a dormitory should be vaccinated.

MCV is 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 is not available.

Meningococcal vaccination is recommended for persons at increased risk for meningococcal disease, including microbiologists who are routinely exposed to isolates of ***N. meningitidis***, military recruits, persons who travel to and U.S. citizens who reside in countries in which ***N. meningitidis*** is hyperendemic or epidemic, persons with terminal complement component deficiency, and persons with functional or anatomic asplenia.

For travelers, vaccination is especially recommended for those visiting countries in the sub-Saharan Africa "meningitis belt" (Ethiopia in the east to Senegal in the west). Epidemics in the meningitis belt usually occur during the dry season (i.e., from December to June). Vaccination is recommended for travelers visiting the region during this time. Vaccination is required by the government of Saudi Arabia for all travelers to Mecca during the annual Hajj. Information concerning geographic areas for which vaccination is recommended can be obtained from the CDC Travelers Health website at http://www.cdc.gov/travel.

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-based rates should be used rather 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., asplenic persons 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 with 7 days of vaccination. Less than 3% of recipients reported these systemic reactions as severe.

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%

As of September 22, 2006 the Vaccine Adverse Event Reporting System (VAERS) received 15 confirmed case reports of Guillain-Barré Syndrome (GBS) in persons 11 to 19 years of age after receipt of MCV vaccine. Symptom onset occurred 2–33 days after vaccination. Data are not sufficient to determine at this time if MCV increases the risk of GBS in persons who receive the vaccine. GBS is a rare illness, and the expected background population rates of GBS are not precisely known. Because ongoing known risk for serious meningococcal disease exists, CDC recommends continuation of current vaccination strategies. Whether receipt of MCV vaccine might increase the risk for recurrence of GBS is unknown. Until this issue is clarified, persons with a history of GBS who are not in a high-risk group for invasive meningococcal disease should not receive MCV.

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

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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Human Papillomavirus

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

Human Papillomavirus

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

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

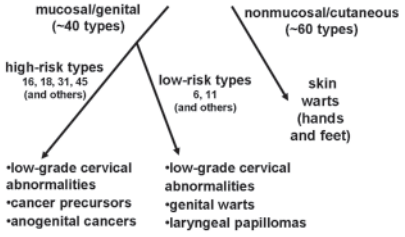
Pathogenesis

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

Human Papillomavirus (HPV)

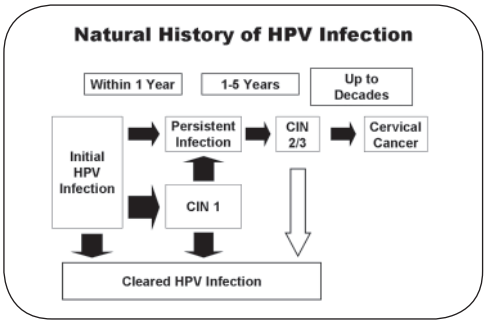
- Small DNA virus
- More than 100 types identified based on the genetic sequence of the outer capsid protein L1
- 40 types infect the mucosal epithelium

Human Papillomavirus Types and Disease Association



HPV-Associated Disease

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



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

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

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

Clinical Features

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

HPV Clinical Features

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

Laboratory Diagnosis

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

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

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

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

Medical Management

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

Epidemiology

Occurrence

HPV infection occurs throughout the world.

Reservoir

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

Transmission

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

Studies of newly acquired HPV infection demonstrate that infection occurs soon after onset of sexual activity. In a prospective study of college women, the cumulative incidence of infection was 40% by 24 months after first sexual intercourse. HPV 16 accounted for 10.4% of infections.

Genital HPV infection also may be transmitted by nonsexual routes, but this appears to be uncommon. Nonsexual routes of genital HPV transmission include transmission from a woman to a newborn infant at the time of birth.

Temporal Pattern

There is no known seasonal variation in HPV infection.

Communicability

HPV is presumably communicable during the acute infection and during persistent infection. This issue is difficult to study because of the inability to culture the virus. Communicability can presumed to be high because of the large number of new infections estimated to occur each year.

HPV Epidemiology

• Reservoir	Human
• Transmission	Direct contact, usually sexual
• Temporal pattern	None
• Communicability	Presumed to be high

Risk Factors

Risk factors for HPV infection are related to sexual behavior, including the number of sex partners, lifetime history of sex partners, and the partners' sexual history. Most studies suggest that young age (less than 25 years) is a risk factor for infection. Results of epidemiologic studies are less consistent for other risk factors, including young age at sexual initiation, inconsistent condom use, number of pregnancies, genetic factors, smoking, lack of circumcision of male partner, and oral contraceptive use

Disease Burden in the United States

HPV Disease Burden in the United States

- Anogenital HPV is the most common sexually transmitted infection in the US
  - –Estimated 20 million currently infected
  - –6.2 million new infections/year
- Common among adolescents and young adults
- More than 80% of sexually active women will have been infected by age 50
- Infection also common in men

Anogenital HPV infection is believed to be the most common sexually transmitted infection in the United States. An estimated 20 million persons are currently infected, and an estimated 6.2 million new HPV infections occur annually. HPV infection is common among adolescents and young adults. Prevalence among adolescent girls is as high as 64%. Up to 75% of new infections occur among persons 15–24 years of age. Modeling estimates suggest that more than 80% of sexually active women will have been infected by age 50.

HPV infection is also common in men. Among heterosexual men in clinic-based studies, prevalence of genital HPV infection is often greater than 20%. Prevalence is highly dependent on the anatomic sites sampled and method of specimen collection.

Cervical Cancer Disease Burden in the United States

- The American Cancer Society estimates that in 2006
  - –9,700 new cervical cancer cases
  - –3,700 cervical cancer deaths
- Almost 100% of these cervical cancer cases will be caused by one of the 40 HPV types that infect the mucosa

The two most common types of cervical cancer worldwide, squamous cell carcinoma followed by adenocarcinoma, are both caused by HPV. The American Cancer Society estimates that in 2006 about 9,700 new cases of cervical cancer will be diagnosed in the United States. Approximately 3,700 women will die as a result of cervical cancer. HPV is believed to be responsible for nearly all of these cases of cervical cancer. HPV types 16 and 18 are associated with 70% of these cancers.

In addition to cervical cancer, HPV is believed to be responsible for 90% of anal cancers, 40% of vulvar, vaginal, or penile cancers, and 12% of oral and pharyngeal cancers.

Population-based estimates, primarily from clinics treating persons with sexually transmitted infections, indicate that about 1% of the sexually active adolescent and adult population in the United States have clinically apparent genital warts. More than 90% of cases of anogenital warts are associated with the low-risk HPV types 6 and 11.

About 4 billion dollars are spent annually on management of sequelae of HPV infections, primarily for the management of abnormal cervical cytology and treatment of cervical neoplasia. This exceeds the economic burden of any other sexually transmitted infection except human immunodeficiency virus.

Prevention

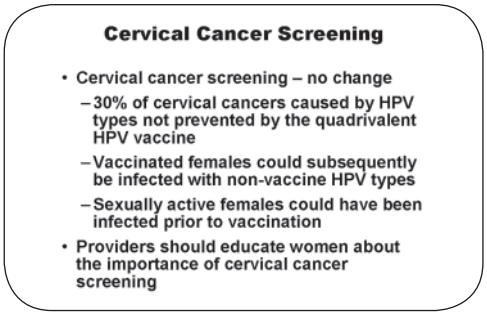
HPV Infection

HPV transmission can be reduced but not eliminated with the use of physical barriers such as condoms. Recent studies demonstrated a significant reduction in HPV infection among young women after initiation of sexual activity when their partners used condoms consistently and correctly. Abstaining from sexual activity (i.e., refraining from any genital contact with another individual) is the surest way to prevent genital HPV infection. For those who choose to be sexually active, a monogamous relationship with an uninfected partner is the strategy most likely to prevent future genital HPV infections.

Cervical Cancer Screening

Most cases and deaths from cervical cancer can be prevented through detection of precancerous changes within the cervix by cervical cytology using the Pap test. Currently available Pap test screening can be done by a conventional Pap or a liquid-based cytology. CDC does not issue recommendations for cervical cancer screening, but various professional groups have published recommendations. The American College of Obstetricians and Gynecologists (ACOG), the American Cancer Society (ACS), and the U.S. Preventive Services Task Force (USPSTF) guidelines recommend that all women should have a Pap test for cervical cancer screening within 3 years of beginning sexual activity or by age 21, whichever occurs first. While the USPSTF recommends a conventional Pap test at least every 3 years regardless of age, ACS and ACOG recommend annual or biennial screening of women younger than age 30, depending on use of conventional or liquid–based cytology. According to these national organizations, women over age 30 with three normal consecutive Pap tests should be screened every 2 to 3 years.

The use of HPV vaccine does not eliminate the need for continued Pap test screening, since 30% of cervical cancers are caused by HPV types not included in the vaccine.



Human Papillomavirus Vaccine

- HPV L1 major capsid protein of the virus is antigen used for immunization
- L1 protein expressed in yeast cells using recombinant technology
- L1 proteins self-assemble into virus-like particles (VLP)
- Noninfectious and nononcogenic

Human Papillomavirus Vaccine

Characteristics

The currently licensed vaccine is a quadrivalent HPV vaccine (Gardasil, Merck). The vaccine antigen is the L1 major capsid protein of HPV, produced by using recombinant DNA technology. The L1 protein is expressed in *Saccharomyces cerevisiae* (yeast) cells, and the protein self-assembles into noninfectious, nononcogenic virus-like-particles (VLP). Each 0.5-mL dose contains 20 µg HPV 6 L1 protein, 40 µg HPV 11 L1 protein, 40 µg HPV 16 L1 protein, and 20 µg HPV 18 L1 protein. The VLPs are adsorbed on 225 µg alum adjuvant. The vaccine also includes sodium chloride, L-histidine, polysorbate 80, sodium borate, and water for injection. The quadrivalent HPV vaccine contains no thimerosal or antibiotics. The vaccine is supplied in single-dose vials and syringes.

Immunogenicity and Vaccine Efficacy

The immunogenicity of the quadrivalent HPV vaccine has been measured by detection of IgG antibody to the HPV L1 by a type-specific immunoassay developed by the manufacturer. In all studies conducted to date, more than 99.5% of participants developed an antibody response to all four HPV types in the vaccine 1 month after completing the three-dose series. At that time interval, antibody titers against HPV types 6, 11, 16, and 18 were higher than those that developed after natural HPV infection.

There is no known serologic correlative of immunity and no known minimal titer determined to be protective. The high efficacy found in the clinical trials to date has precluded identification of a minimum protective antibody titer. Further follow-up of vaccinated cohorts may allow determination of serologic correlates of immunity in the future.

HPV Vaccine Efficacy*

Endpoint	Efficacy
HPV 16/18-related CIN2/3 or AIS	100
HPV 6/11/16/18 related CIN	95
HPV 6/11/16/18 related genital warts	99

*Among 16-26 year old females. CIN – cervical intraepithelial neoplasia; AIS – adenocarcinoma *in situ*

HPV vaccine has been found to have high efficacy for prevention of HPV vaccine type–related persistent infection, vaccine type–related CIN, CIN2/3, and external genital lesions in women 16–26 years of age. Clinical efficacy against cervical disease was determined in two double-blind, placebo-controlled trials, using various endpoints. Vaccine efficacy was 100% for prevention of HPV 16 or 18–related CIN 2/3 or adenocarcinoma in-situ (AIS). Efficacy against any CIN due to HPV 6, 11, 16, or 18 was 95%. Efficacy against HPV 6, 11, 16 or 18–related genital warts was 99%.

Although high efficacy among females without evidence of infection with vaccine HPV types was demonstrated in clinical trials, there was no evidence of efficacy against disease caused by vaccine types with which participants were infected at the time of vaccination. Participants infected

with one or more vaccine HPV types prior to vaccination were protected against disease caused by the other vaccine types. However, prior infection with one HPV type did not diminish efficacy of the vaccine against other vaccine HPV types.

There is no evidence that the vaccine protects against disease due to non-vaccine HPV types or provides a therapeutic effect against cervical disease or genital warts present at the time of vaccination.

A subset of participants in the phase II HPV vaccine study has been followed for 60 months post-dose 1 with no evidence of waning protection. Study populations will continue to be followed for any evidence of waning immunity.

HPV vaccine has been shown to be immunogenic and safe in males. However, no clinical efficacy data are available for males. These studies are in progress.

HPV Vaccine Efficacy

- High efficacy among females without evidence of infection with vaccine HPV types
- No evidence of efficacy against disease caused by vaccine types with which participants were infected at the time of vaccination
- Prior infection with one HPV type did not diminish efficacy of the vaccine against other vaccine HPV types

Vaccination Schedule and Use

As of January 2007, ACIP recommendations for use of HPV vaccine have not been published. Recommendations included here are provisional until published in the *Morbidity and Mortality Weekly Report*.

Quadrivalent HPV vaccine is licensed by the Food and Drug Administration for use among females 9–26 years of age. The recommended age for routine vaccination in the United States is 11–12 years. The vaccine can be given as young as 9 years of age at the discretion of the clinician. The vaccine should be given at the same visit as other vaccines recommended for persons of this age (e.g., Tdap, meningococcal conjugate, hepatitis B).

At the beginning of a vaccination program, there will be females older than 12 years of age who did not have the opportunity to receive vaccine at age 11–12 years. Catch-up vaccination is recommended for females 13 through 26 years of age who have not been previously vaccinated or who have not completed the full series. Ideally, vaccine should be administered before potential exposure to HPV through sexual contact; however, females who may have already been exposed to HPV should be vaccinated. Sexually active females who have not been infected with any of the HPV vaccine types will receive full benefit from vaccination. Vaccination will provide less benefit to females if they have already been infected with one or more of the four HPV vaccine types. However, it is not possible for a clinician to assess the extent to which sexually active females would

Routine HPV Vaccination Recommendations*

- ACIP recommends routine vaccination of females 11-12 years of age *
- The vaccination series can be started as young as 9 years of age at the clinician's discretion
- Catch-up vaccination recommended for females 13 through 26 years of age

*Provisional ACIP recommendations, June 2006

benefit from vaccination, and the risk of HPV infection may continue as long as persons are sexually active. Pap testing or screening for HPV DNA or HPV antibody is not recommended prior to vaccination at any age.

HPV Vaccination Schedule

- Routine schedule is 0, 2, 6 months
- Minimum intervals
  - –4 weeks between doses 1 and 2
  - –12 weeks between doses 2 and 3
- Do not restart the series if the schedule is interrupted
- Administer at same visit as other age-appropriate vaccines (e.g., Tdap, MCV)

HPV vaccine is administered in a three-dose series administered by intramuscular injection. The second and third doses should be administered 2 and 6 months after the first dose. The minimum interval between the first and second doses is 4 weeks. The minimum interval between the second and third dose of vaccine is 12 weeks. Doses administered at an interval shorter than the minimum interval should not be counted as valid and should be repeated.

If the HPV vaccine schedule is interrupted, the vaccine series does not need to be restarted. If the series is interrupted after the first dose, the second dose should be given as soon as possible, and the second and third doses should be separated by an interval of at least 12 weeks. If only the third dose is delayed, it should be administered as soon as possible.

Although no data are available yet on administration of quadrivalent HPV vaccine with vaccines other than hepatitis B vaccine, the vaccine contains only HPV capsid protein and has no components that have been found to adversely affect safety or efficacy of other vaccinations. The vaccine can be administered at the same visit as other age-appropriate vaccines, such as Tdap and quadrivalent meningococcal conjugate (MCV4) vaccines. Administering all indicated vaccines at a single visit increases the likelihood that adolescents and young adults will receive each of the vaccines on schedule. Each vaccine should be administered using a separate syringe at a different anatomic site.

HPV vaccine is not approved for use among females younger than 9 years or older than 26 years of age. Use of the vaccine in females younger than 9 years or older than 26 years is not recommended. Studies with females older than 26 years of age are ongoing. There are no current studies among children younger than 9 years of age.

Quadrivalent HPV Vaccine

- HPV vaccine is not licensed for use among males
  - –Efficacy data are not available
  - –Off-label use not recommended
- Efficacy studies in males in progress

Quadrivalent HPV vaccine is not licensed for use among males, and off-label use among males is not recommended. While data on immunogenicity and safety are available for 9–15-year-old males, there are no data on efficacy in males at any age. Efficacy studies among males are under way.

Females who have an equivocal or abnormal Pap test could be infected with any of more than 40 high-risk or low-risk genital HPV types. It is unlikely that such females would be infected with all four HPV vaccine types, and they may not

be infected with any HPV vaccine type. Women younger than 27 years with a previously abnormal Pap test may be vaccinated. Women should be advised that data do not indicate the vaccine will have any therapeutic effect on existing HPV infection or cervical lesions.

Females who have a positive HPV DNA test (Hybrid Capture 2®)done in conjunction with a Pap test could be infected with any of 13 high-risk types. This assay does not identify specific HPV types, and testing for specific HPV types is not done routinely in clinical practice. Women younger than 27 years with a positive HPV DNA test may be vaccinated. HPV DNA testing is not a prerequisite for vaccination. Women should be advised that the vaccine will not have a therapeutic effect on existing HPV infection or cervical lesions.

A history of genital warts or clinically evident genital warts indicate infection with HPV, most often type 6 or 11. However, these females may be infected with HPV types other than the vaccine types, and therefore they may receive HPV vaccine if they are in the recommended age group. Women with a history of genital warts should be advised that data do not indicate the vaccine will have any therapeutic effect on existing HPV infection or genital warts.

HPV Vaccine Special Situations*

- Vaccine can be administered
  - –Equivocal or abnormal Pap test
  - –Positive HPV DNA test
  - –Genital warts
  - –Immunosuppression
  - –Breastfeeding

Because quadrivalent HPV vaccine is a subunit vaccine, it can be administered to females who are immunosuppressed because of disease or medications. However, the immune response and vaccine efficacy might be less than that in persons who are immunocompetent. Women who are breastfeeding may receive HPV vaccine.

Adverse Reactions Following Vaccination

The most common adverse reactions reported during clinical trials of HPV vaccine were local reactions at the site of injection. These were most commonly pain (84%), swelling (25%), and erythema (25%). The majority of injection-site adverse experiences reported by recipients of quadrivalent HPV vaccine were mild to moderate in intensity. Fever was reported within 15 days of vaccination by 10% of vaccine recipients and 9% of placebo recipients. No serious adverse reactions have been reported.

HPV Vaccine Adverse Reactions

• Local reactions (pain, swelling)	84%
• Fever	10%*
• No serious adverse reactions reported	

*similar to reports in placebo recipients (9%)

A variety of systemic adverse reactions were reported by vaccine recipients, including nausea, dizziness, myalgia and malaise. However, these symptoms occurred with equal frequency among both vaccine and placebo recipients.

HPV Vaccine
Contraindications and Precautions

- Contraindication
  - Severe allergic reaction to a vaccine component or following a prior dose
- Precaution
  - Moderate or severe acute illnesses (defer until symptoms improve)

Vaccination During Pregnancy
Provisional Recommendation

- Initiation of the vaccine series should be delayed until after completion of pregnancy
- If a woman is found to be pregnant after initiating the vaccination series, remaining doses should be delayed until after the pregnancy
- If a vaccine dose has been administered during pregnancy, there is no indication for intervention
- Women vaccinated during pregnancy should be reported to Merck registry (800.986.8999)

HPV Vaccine
Storage and Handling

- Store at 36° – 46°F (2° – 8°C)
- Protect from light
- Administer immediately after removing from refrigeration
- Do not expose to freezing temperature

Contraindications and Precautions to Vaccination

A severe allergic reaction (acute respiratory distress or collapse) to a vaccine component or following a prior dose of HPV vaccine is a contraindication to receipt of HPV vaccine. A moderate or severe acute illness is a precaution to vaccination, and vaccination should be deferred until symptoms of the acute illness improve. A minor acute illness (e.g., diarrhea or mild upper respiratory tract infection, with or without fever) is not a reason to defer vaccination.

HPV vaccine is not recommended for use during pregnancy. The vaccine has not been associated with adverse outcomes of pregnancy or with adverse effects on the developing fetus. However, data on vaccination during pregnancy are limited. Until further information is available, initiation of the vaccine series should be delayed until after completion of the pregnancy. If a woman is found to be pregnant after initiating the vaccination series, the remainder of the three-dose regimen should be delayed until after completion of the pregnancy. If a vaccine dose has been administered during pregnancy, no intervention is indicated. A vaccine in pregnancy registry has been established; patients and healthcare providers are urged to report any exposure to quadrivalent HPV vaccine during pregnancy by calling (800) 986-8999.

Vaccine Storage and Handling

HPV vaccine should be stored continuously at 35°–46°F (2°–8°C) and should be protected from light. The vaccine should be removed from refrigeration immediately before administration. The vaccine must not be exposed to freezing temperature. Vaccine exposed to freezing temperature should never be administered.

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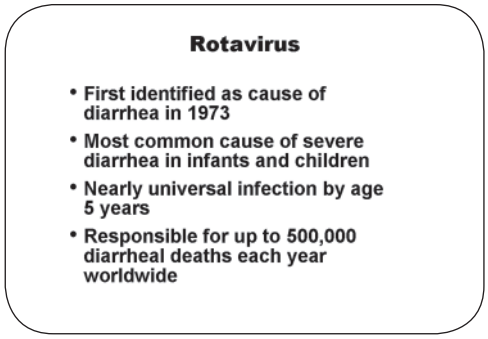
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Human Papillomavirus

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Rotavirus

Diarrheal disease has been recognized in humans since antiquity. Until the early 1970s, a bacterial, viral, or parasitic etiology of diarrheal disease in children could be detected in fewer than 30% of cases. In 1973, Bishop and colleagues observed a virus particle in the intestinal tissue of children with diarrhea by using electron micrography. This virus was subsequently called "rotavirus" because of its similarity in appearance to a wheel (rota is Latin for wheel). By 1980, rotavirus was recognized as the most common cause of severe gastroenteritis in infants and young children in the United States. It is now known that infection with rotavirus is nearly universal, with almost all children infected by 5 years of age. Rotavirus is responsible for 20–60 deaths per year in the United States and up to 500,000 deaths from diarrhea worldwide. A vaccine to prevent rotavirus gastroenteritis was first licensed in August 1998 but was withdrawn in 1999 because of its association with intussusception. A second-generation vaccine was licensed in 2006.

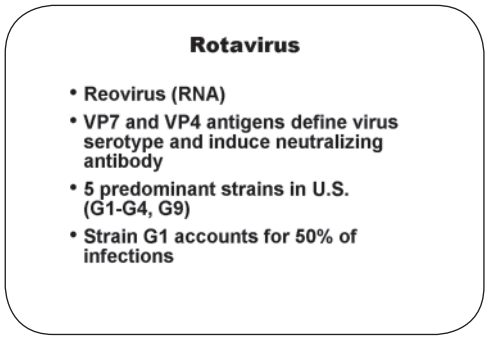


Rotavirus

Rotavirus is a double-stranded RNA virus of the family *Reoviridae*. The virus is composed of three concentric shells that enclose 11 gene segments. The outermost shell contains two important proteins—VP7, or G-protein, and VP4, or P-protein. VP7 and VP4 define the serotype of the virus and induce neutralizing antibody that is probably involved in immune protection. Five strains of rotavirus (G1–4, G9) account for 90% of isolates from children younger than 5 years in the United States. Of these, the G1 strain accounts for more than 80% of isolates.

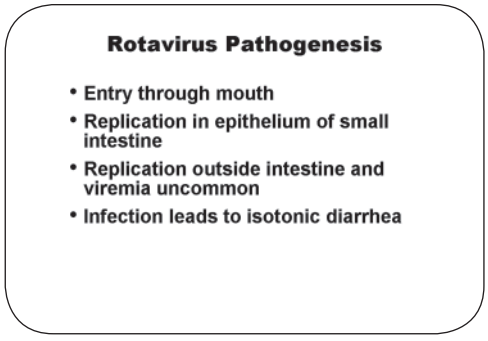
Rotavirus is very stable and may remain viable in the environment for weeks or months if not disinfected.

Rotaviruses cause infection in many species of mammals, including cows and monkeys. These animal strains are antigenically distinct from those causing human infection, and they rarely cause infection in humans.



Pathogenesis

The virus enters the body through the mouth. Viral replication occurs in the villous epithelium of the small intestine. Replication outside the small intestine and systemic spread of the virus (viremia) are believed to be uncommon in immunocompetent persons. Infection may result in decreased intestinal absorption of sodium, glucose, and water, and decreased levels of intestinal lactase, alkaline phosphatase, and sucrase activity, and may lead to isotonic diarrhea.



Rotavirus Immunity

- Antibody against VP7 and VP4 probably important for protection
- First infection usually does not lead to permanent immunity
- Reinfection can occur at any age
- Subsequent infections generally less severe

The immune correlates of protection from rotavirus are poorly understood. Serum and mucosal antibodies against VP7 and VP4 are probably important for protection from disease. Cell-mediated immunity probably plays a role in recovery from infection and in protection.

Recovery from a first rotavirus infection usually does not lead to permanent immunity. After a single natural infection, 40% of children are protected against any subsequent rotavirus infection, 75% are protected against rotavirus diarrhea, and 88% are protected against severe diarrhea. Reinfection can occur at any age. Subsequent infections confer progressively greater protection and are generally less severe than the first. Recurrent rotavirus infections affect persons of all ages. Recurrent infections are usually asymptomatic or result in mild diarrhea that may be preceded or accompanied by vomiting and low-grade fever.

Clinical Features

Rotavirus Clinical Features

- Incubation period 1-3 days
- Variable clinical presentation–asymptomatic to severe diarrhea
- First infection after age 3 months generally most severe
- Illness not specific for rotavirus
- Confirmation requires laboratory testing

The incubation period for rotavirus diarrhea is 1–3 days. The clinical manifestations of infection vary and depend on whether it is the first infection or reinfection. Infection may be asymptomatic, may cause self-limited watery diarrhea, or may result in severe dehydrating diarrhea with fever and vomiting. The first infection after 3 months of age is generally the most severe. Up to one-third of infected children may have a temperature greater than 102°F (39°C). The gastrointestinal symptoms generally resolve in 3–7 days.

The clinical features and stool characteristics of rotavirus diarrhea are nonspecific, and similar illness may be caused by other pathogens. As a result, confirmation of a diarrheal illness as rotavirus requires laboratory testing.

Complications

Rotavirus Complications

- Severe diarrhea
- Dehydration
- Electrolyte imbalance
- Metabolic acidosis
- Immunodeficient children may have more severe or persistent disease

Rotavirus infection in infants and young children can lead to severe diarrhea, dehydration, electrolyte imbalance, and metabolic acidosis. Immunodeficient children may have more severe or persistent disease and may have evidence of abnormalities in multiple organ systems, particularly the kidney and liver.

Laboratory Diagnosis

The most widely available method for confirmation of rotavirus infection is detection of rotavirus antigen in stool by enzyme immunoassay (EIA). Several commercial test kits are available that detect an antigen common to human rotaviruses. These kits are simple to use, inexpensive, and very sensitive. Other techniques (such as electron microscopy, reverse transcription polymerase chain reaction, nucleic acid hybridization,

sequence analysis, and culture) are used primarily in research settings. Rotavirus antigen has also been identified in the serum of patients 3–7 days after disease onset, but at present, routine diagnostic testing is based primarily on testing of fecal specimens.

Epidemiology

Occurrence

Rotavirus occurs throughout the world. The prevalence of rotavirus strains varies by geographic area, and strains not included in the vaccine are present in some parts of the world.

Rotavirus Epidemiology

• Reservoir	Human
• Transmission	Fecal-oral, fomites
• Temporal pattern	Fall and winter (temperate areas)
• Communicability	2 days before to 10 days after onset

Reservoir

The reservoir of rotavirus is the gastrointestinal tract and stool of infected humans. Although rotavirus infection occurs in many nonhuman mammals, transmission of animal rotaviruses to humans is believed to be rare and probably does not lead to clinical illness. Although immunodeficient persons may shed rotavirus for a prolonged period, a true carrier state has not been described.

Transmission

Rotaviruses are shed in high concentration in the stool of infected persons. Transmission is by fecal-oral spread, both through close person-to-person contact and by fomites (such as toys and other environmental surfaces contaminated by stool). Rotaviruses are also probably transmitted by other modes such as fecally contaminated food and water and respiratory droplets.

Temporal Pattern

In temperate climates, disease is more prevalent during cooler months. In the United States, annual epidemic peaks usually progress from the Southwest during November and December and spread to the Northeast by April and May. The reason for this seasonal pattern is unknown. In tropical climates, the disease is less seasonal than in temperate areas.

Communicability

Rotavirus is highly communicable, as evidenced by the nearly universal infection of children by age 5 years. Infected persons shed large quantities of virus in their stool beginning 2 days before the onset of diarrhea and for up to 10 days after onset of symptoms. Rotavirus may be detected in the stool of immunodeficient persons for more than 30 days after infection. Spread within families, institutions, hospitals, and child care settings is common.

Rotavirus Disease Burden in the United States

- Estimated 2.7 million cases per year
- 95% of children infected by 5 years of age
- Highest incidence among children 3 to 35 months of age
- Responsible for 5%-10% of all gastroenteritis episodes among children younger than 5 years of age

Secular Trends in the United States

Rotavirus infection is not nationally notifiable in the United States. Estimates of incidence and disease burden are based on special surveys, cohort studies, and hospital discharge data.

Rotavirus infection is nearly universal. An estimated 2.7 million cases occur each year in the United States alone, and 95% of children experience at least one rotavirus infection by age 5 years. The incidence of rotavirus is similar in developed and developing countries, suggesting that improved sanitation alone is not sufficient to prevent the infection.

Infants younger than 3 months of age have relatively low rates of rotavirus infection, probably because of passive maternal antibody, and possibly breastfeeding. The incidence of clinical illness is highest among children 3 to 35 months of age. Rotavirus infection of adults is usually asymptomatic but may cause diarrheal illness.

Rotavirus Disease in the United States

- Annually responsible for:
  - —More than 400,000 physician visits
  - —More than 200,000 emergency dept visits
  - —55,000-70,000 hospitalizations
  - —20-60 deaths
- Annual direct and indirect costs are estimated at approximately $1 billion

In the United States, rotaviruses are responsible for 5%–10% of all gastroenteritis episodes among children younger than 5 years of age. However, they are the most common cause of severe diarrheal disease and account for a higher proportion of severe episodes leading to clinic or hospital visits. Rotavirus accounts for 30%–50% of all hospitalizations for gastroenteritis among U.S. children younger than 5 years of age, and more than 70% of hospitalizations for gastroenteritis during the seasonal peaks.

Rotavirus infection is responsible for more than 400,000 physician visits, more than 200,000 emergency department (ED) visits, 55,000–70,000 hospitalizations each year, and 20–60 deaths. Annual direct and indirect costs are estimated at approximately $1 billion, primarily due to the cost of time lost from work to care for an ill child.

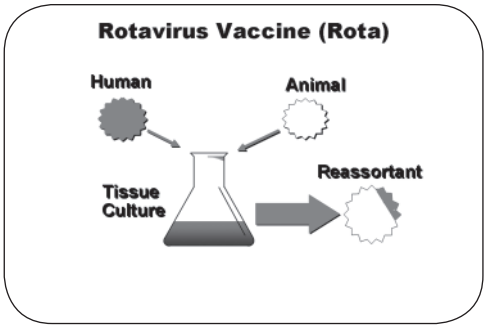
Risk Groups for Rotavirus Diarrhea

- Groups with increased exposure to virus
  - —Children in child care centers
  - —Children in hospital wards (nosocomial rotavirus)
  - —Caretakers, parents of these children
  - —Children, adults with immunodeficiency-related diseases (e.g. SCID, HIV, bone marrow transplant)

Groups at increased risk for rotavirus infection are those with increased exposure to virus. This includes children who attend child care centers, children in hospital wards (nosocomial rotavirus), caretakers and parents of children in child care or hospitals, and children and adults with immunodeficiency-related diseases (e.g., Severe Combined Immunodeficiency Disease (SCID), HIV, bone marrow transplant).

Rotavirus Vaccine

The first rotavirus vaccines were derived from either bovine (cow) or rhesus (monkey) origin. Studies demonstrated that these live oral vaccines could prevent rotavirus diarrhea in young children, but efficacy varied widely. Because immunity to G (VP7) and P (VP4) proteins was associated with disease protection and recovery, new live virus vaccines were developed that incorporated G proteins or both G and P proteins for each of the predominant serotypes.



The process by which these vaccine viruses were created is called genetic reassortment. Tissue culture cells were infected with two different rotavirus strains—a nonhuman "parent" strain and a human strain that contained the VP7 gene of a predominant serotype. When the viruses replicated, the offspring viruses had various combinations of gene segments from the two strains. Offspring were selected that contained the gene segment coding for a human G (VP7) serotype. The remainder of the gene was identical to the parent nonhuman strain. By this process, viruses—known as reassortants—were developed that expressed human G1, G2, G3, and G4 serotypes of the VP7 antigen.

In 1998, a rhesus-based tetravalent rotavirus vaccine (RRV-TV, Rotashield) was licensed and recommended for routine immunization of U.S. infants. However, RRV-TV was withdrawn from the U.S. market within one year of its introduction because of its association with intussusception. The risk of intussusception was most elevated (more than a 20-fold increase) within 3–14 days after receipt of the first dose of RRV-TV, with a smaller (approximately 5-fold) increase in risk within 3–14 days after the second dose. Overall, the risk associated with the first dose of RRV-TV was estimated to be about one case per 10,000 vaccine recipients. Some researchers have suggested that the risk of intussusception associated with RRV-TV was age-dependent and that the absolute number of intussusception events, and possibly the relative risk of intussusception associated with the first dose of RRV-TV, increased with increasing age at vaccination.

Characteristics

In February 2006, the Food and Drug Administration approved a new rotavirus vaccine (Rota), RotaTeq, produced by the Merck Vaccine Division. RotaTeq is a live, oral vaccine that contains five reassortant rotaviruses developed from human and bovine parent rotavirus strains. Four reassortant rotaviruses express one of the outer proteins (G1, G2, G3, or G4) from the human rotavirus strain and the attachment protein (P7[5]) from the bovine rotavirus parent strain. The fifth reassortant virus expresses the attachment protein from the human rotavirus strain and the outer protein (G6) from the bovine rotavirus parent strain. The parent

bovine rotavirus strain Wistar Calf 3 (WC3) was isolated in 1981 from a calf with diarrhea in Chester County, Pennsylvania. The virus was passaged 12 times in African green monkey kidney cells. The reassortants are propagated in Vero cells using standard tissue culture techniques.

Rotavirus Vaccine (RotaTeq)

- Approved by FDA in February 2006
- Contains five reassortant rotaviruses developed from human and bovine parent rotavirus strains
- Vaccine viruses suspended in a solution of buffer (sodium citrate and phosphate) and stabilizer
- Contains no preservatives or thimerosal

RotaTeq consists of the five human–bovine reassortants suspended in a solution of buffer (sodium citrate and phosphate) and stabilizer (sucrose). Each 2-mL vial of vaccine contains approximately 2 x 10^6 infectious units of each of the five reassortant strains. The vaccine formulation contains sucrose, sodium citrate, sodium phosphate monobasic monohydrate, sodium hydroxide, polysorbate 80, and tissue culture media. Trace amounts of fetal bovine serum might be present. The vaccine contains no preservatives or thimerosal.

Fecal shedding of vaccine virus was evaluated in a subset of persons enrolled in the phase III trials. Vaccine virus was shed by 32 (8.9%) of 360 infants after dose 1, but none of 249 and 385 infants after doses 2 and 3, respectively. Shedding was observed as early as 1 day and as late as 15 days after a dose. The potential for horizontal transmission of vaccine virus was not assessed through epidemiologic studies.

Rotavirus Vaccine Efficacy

- Phase III trials included more than 70,000 infants in 11 countries
- Efficacy
  - –All rotavirus disease – 74%
  - –Severe rotavirus disease – 98%
  - –Significantly reduced office and ED visits and hospitalization for rotavirus gastroenteritis
- Efficacy of fewer than 3 doses is not known

N Eng J Med 2006;354:23-33

Immunogenicity and Vaccine Efficacy

Phase III clinical trials of Rotateq immunogenicity and efficacy have involved more than 70,000 infants 6–12 weeks of age in 11 countries.

The immune correlates of protection from rotavirus infection and disease are not fully understood. In clinical trials, a rise in titer of rotavirus group-specific serum IgA antibodies was used as one of the measures of immunogenicity. Sera were collected before vaccination and approximately 2 weeks after the third dose. Seroconversion was defined as a threefold or greater rise in antibody titer from baseline. Seroconversion rates for IgA antibody to rotavirus were 93%–100% among 439 vaccine recipients versus 12%–20% among 397 placebo recipients.

After completion of a three-dose regimen, the efficacy of rotavirus vaccine against rotavirus gastroenteritis of any severity was 74%, and against severe rotavirus gastroenteritis (defined by severity of fever, vomiting, diarrhea and changes in behavior) was 98%. Vaccine efficacy varied by rotavirus serotype.

In a large study, the efficacy of rotavirus vaccine against rotavirus gastroenteritis requiring office visits was evaluated among 5,673 persons, and efficacy against rotavirus gastroenteritis requiring ED visits and hospitalizations was evaluated among 68,038 persons during the first 2 years of

life. Rotavirus vaccine reduced the incidence of office visits by 86%, ED visits by 94%, and hospitalizations for rotavirus gastroenteritis by 96%.

The efficacy of fewer than three doses is not known.

Duration of Immunity

The duration of immunity from rotavirus vaccine is not known. At least one clinical trial has demonstrated that protection lasts through at least 2 rotavirus seasons, although efficacy was somewhat lower in the second season than in the first.

Vaccination Schedule and Use

The Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination of all infants without contraindications with three doses of rotavirus vaccine administered orally at ages 2, 4, and 6 months. The minimum age for the first dose is 6 weeks. The first dose should be administered between 6 and 12 weeks of age (that is, until age 13 weeks). Vaccination should not be initiated for infants older than 12 weeks because of insufficient data on safety of the first dose of rotavirus vaccine in older infants.

Rotavirus Vaccine Recommendations

- Routine immunization of all infants without contraindications
- Administered at 2, 4, and 6 months of age
- Minimum age of first doses is 6 weeks
- First dose should be administered between 6 and 12 weeks of age (until age 13 weeks)
- Do not initiate series after 12 weeks of age

All three doses should routinely be separated by 2 months. However, the minimum interval between doses may be a short as 4 weeks if an accelerated schedule is required. Special effort should be made to immunize infants before the winter rotavirus season, and the use of an accelerated schedule may facilitate this effort.

Rotavirus Vaccine Recommendations

- Minimum interval between doses is 4 weeks
- Maximum age for ANY dose is 32 weeks
- Do not administer on or after age 32 weeks, even if fewer than three doses have been administered

The maximum age for any dose of rotavirus vaccine is 32 weeks because of insufficient data on the safety and efficacy of rotavirus vaccine in infants after this age. Rotavirus vaccine should not be administered on or after age 32 weeks, even if fewer than three doses have been administered.

Rotavirus vaccine may be administered simultaneously with all other vaccines that are routinely given at the same ages (hepatitis B, DTaP, IPV, Hib, PCV).

Rotavirus Vaccine Recommendations

- Administer simultaneously with all other indicated vaccines
- Breastfeeding infants should be vaccinated on usual schedule
- Vaccinate infants who have recovered from documented rotavirus infection
- Do not repeat dose if infant spits out or regurgitates vaccine- administer remaining doses on schedule

Breastfeeding does not appear to diminish immune response to three doses of vaccine. Children who are being breastfed should be vaccinated on schedule.

Infants who have recovered from documented rotavirus infections may not be immune to all five serotypes present in the vaccine. These infants should complete the three-dose vaccination series by 32 weeks of age.

Data on the safety of administering a dose higher than the recommended dose, or on the efficacy of a partial dose are very limited. As a result, a second dose of rotavirus vaccine should not be administered to an infant who regurgitates, spits out some or all of the dose, or vomits during or after administration of vaccine. The infant should receive the remaining recommended doses, if needed, on the usual schedule.

Adverse Reactions Following Vaccination

Intussusception

The risk for intussusception was evaluated in more than 70,000 infants enrolled in phase III efficacy trials. During the 42 days after vaccination six cases of intussusception were observed in the vaccine group and five cases in the placebo group. There was no evidence, regardless of dose, of clustering of cases of intussusception within 7–14 days postvaccination, the period of greatest risk for intussusception associated with the RRV-TV vaccine. For the 1-year follow-up period after administration of the first dose, 13 cases of intussusception were observed in the vaccine group and 15 cases of intussusception in the placebo group (relative risk: 0.9).

Rotavirus Vaccine and Intussusception

	Vaccine Recipients	Placebo Recipients
Within 42 days of vaccination	6 cases	5 cases
Within 1 year of vaccination	13 cases	15 cases

New Eng J Med 2006;354:23-33

Other Adverse Events

In the 42-day period after vaccination, vaccine recipients had a small increased risk of certain symptoms compared with placebo recipients, including vomiting (15% versus 14%), diarrhea (24% versus 21%), nasopharyngitis (7% versus 6%), otitis media (15% versus 13%), bronchospasm (1.1% versus 0.7%). Among vaccine and placebo recipients, the incidence of reported episodes of fever (43% versus 43%, respectively) and bloody stool (0.5% versus 0.3%, respectively) was similar.

Rotavirus Vaccine Adverse Reactions

- Vomiting 15%
- Diarrhea 24%
- Nasopharyngitis 7%
- Fever 43%
- No serious adverse reactions reported

MMWR 2006;55(RR-12):1-13

Contraindications and Precautions to Vaccination

Rotavirus vaccine is contraindicated for infants who are known to have had a severe allergic (anaphylactic) reaction to a vaccine component or following a prior dose of vaccine.

Rotavirus Vaccine Contraindications

- Severe allergic reaction to a vaccine component or following a prior dose of vaccine

Precaution conditions are those that may increase the chance of a vaccine adverse reaction or reduce the efficacy of the vaccine. In general, infants with precautions to vaccination, described below, should not receive the vaccine until the condition improves unless the benefit of vaccination outweighs the risk of an adverse reaction. The decision to withhold rotavirus vaccine if a precaution is present means that the infant will be infected with wild-type rotavirus,

which is more likely to cause severe illness than the attenuated vaccine virus.

Clinicians should consider the potential risks and benefits of administering rotavirus vaccine to infants with known or suspected altered immunocompetence. Children and adults who are immunocompromised because of congenital immunodeficiency, hematopoietic transplantation, or solid organ transplantation sometimes experience severe, prolonged, and even fatal rotavirus gastroenteritis. However, no safety or efficacy data are available regarding administration of rotavirus vaccine to infants who are or are potentially immunocompromised due to either disease or drugs (including HIV infection or high-dose systemic corticosteroids for more than 2 weeks). Data from the clinical trials are insufficient to support administration of rotavirus vaccine to infants with indeterminant HIV status who are born to mothers with HIV/AIDS.

Rotavirus Vaccine Precautions*

- Altered immunocompetence
- Recent receipt of blood product
- Acute, moderate to severe gastroenteritis or other acute illness
- Pre-existing chronic GI disease
- Infants with history of intussusception

*the decision to vaccinate if a precaution is present should be made on a case-by-case risk and benefit basis

The effect of recent receipt of an antibody-containing blood product on the efficacy of rotavirus vaccine is unknown. However, ACIP recommends deferral of vaccination for infants who have received an antibody-containing product, including blood and immunoglobulin, for 6 weeks after receipt of the blood product. However, if the 6-week deferral would cause the first dose of rotavirus vaccine to be scheduled at an age older than 12 weeks, a shorter deferral interval should be used to ensure the first dose is administered before age 13 weeks.

Usually, rotavirus vaccine should not be administered to infants with acute, moderate to severe gastroenteritis or other acute illness until the condition improves. However, infants with mild acute gastroenteritis can be vaccinated, particularly if the delay in vaccination will delay the first dose of vaccine until 13 weeks of age or older.

The safety and efficacy of rotavirus vaccine in children with pre-existing chronic gastrointestinal (GI) conditions, such as congenital malabsorption syndromes, Hirschsprung disease, or short-gut syndrome, has not been determined. The decision to vaccinate children with these conditions must be made on a case-by-case basis.

Additional postlicensure surveillance data are required to confirm that rotavirus vaccine is not associated with intussusception at a lower rate than would have been detected in prelicensure trials. In addition, data suggest that infants with a history of intussusception might be at higher risk for a repeat episode than other infants. Therefore, until postlicensure data on the safety of rotavirus vaccine are available, the risks for and the benefits of vaccination should be

considered when vaccinating infants with a previous episode of intussusception.

Rotavirus Vaccine and Preterm Infants

- Few data available
- Safety and efficacy of rotavirus vaccine appear to be similar for preterm and term infants
- ACIP considers that the benefits of rotavirus vaccine vaccination of preterm infants outweigh the theoretical risks

Practitioners should consider the potential risks for and benefits of vaccinating preterm infants against rotavirus. Limited data suggest that preterm infants are at increased risk for hospitalization from viral gastroenteritis during their first year of life. In clinical trials, the safety and efficacy of rotavirus vaccine appear to be similar for preterm and term infants, although a relatively small number of preterm infants have been evaluated. The lower level of maternal antibody to rotaviruses in very low birthweight, preterm infants theoretically could increase the risk for adverse reactions from rotavirus vaccine. ACIP supports vaccination of preterm born infants if they are at least 6 weeks of age, are being or have been discharged from the hospital nursery, and are clinically stable. Until further data are available, ACIP considers that the benefits of vaccination of preterm infants with rotavirus vaccine outweigh the theoretical risks.

Immunosuppressed Household Contacts of Rotavirus Vaccine Recipients

- Protection of the immunocompromised household member afforded by vaccination of young children in the household outweighs the small risk for transmitting vaccine virus to the immunocompromised household member
- Household should employ measures such as good handwashing after contact with the feces of the vaccinated infant

Infants living in households with persons who have or are suspected of having an immunodeficiency disorder or impaired immune status can be vaccinated. The majority of experts believe the protection of the immunocompromised household member afforded by vaccination of young children in the household outweighs the small risk for transmitting vaccine virus to the immunocompromised household member and any subsequent theoretical risk for vaccine virus–associated disease. To minimize potential virus transmission, all members of the household should employ measures such as good handwashing after contact with the feces of the vaccinated infant (e.g., after changing a diaper). Infants living in households with a pregnant woman can be vaccinated.

Vaccine Storage and Handling

Rotavirus Vaccine Storage and Handling

- Provided as a single 2-mL oral dose in a buffered stabilizer solution
- Store at 35°-46°F (2°-8°C)
- Shelf life of properly stored vaccine is 24 months
- Do not freeze
- Administer as soon as possible after being removed from refrigeration

RotaTeq is provided in a squeezable plastic dosing tube with a twist-off cap designed to allow for the vaccine to be administered directly to infants by mouth. Each tube contains a single 2-mL dose of the vaccine as a liquid buffered stabilizer solution that is pale yellow in color but might have a pink tint. This formulation protects the vaccine virus from gastric acid and stabilizes the vaccine. The vaccine must be stored at refrigerator temperatures (35°–46°F [2°–8°C]). The shelf life of properly stored vaccine is 24 months. The vaccine must not be frozen. RotaTeq should be administered as soon as possible after being removed from refrigeration. Additional information on stability under conditions other than those recommended is available from the manufacturer at 800-637-2590.

Rotavirus Surveillance

Rotavirus gastroenteritis is not a reportable disease in the United States, and testing for rotavirus infection is not always performed when a child seeks medical care for acute gastroenteritis. Establishing rotavirus disease surveillance systems that are adequately sensitive and specific to document the effectiveness of vaccination programs will be necessary. National surveillance systems for rotavirus infections include review of national hospital discharge databases for rotavirus-specific or rotavirus-compatible diagnoses and reports of rotavirus isolation from a sentinel system of laboratories and surveillance in three sites that participate in the New Vaccine Surveillance Network. At state and local levels, additional surveillance efforts at sentinel hospitals or by review of hospital discharge databases will be necessary to monitor the impact of the vaccination program. Special studies (e.g., case-control studies and retrospective cohort studies) will be needed to confirm the effectiveness of rotavirus vaccine in routine programmatic use.

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APPENDIX A

Schedules and Recommendations

Immunization Schedules on the Web. A-1

Childhood Immunization Schedule 2007 . . . . . A-2

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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 . . .

Appendix A

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

Recommended Immunization Schedule for Ages 0–6 Years UNITED STATES • 2007

Vaccine ▼ / Age ▶	Birth	1 month	2 months	4 months	6 months	12 months	15 months	18 months	19–23 months	2–3 years	4–6 years
Hepatitis B[1]	HepB	HepB		*see footnote 1*	HepB				HepB Series		
Rotavirus[2]			Rota	Rota	Rota						
Diphtheria, Tetanus, Pertussis[3]			DTaP	DTaP	DTaP		DTaP				DTaP
Haemophilus influenzae type b[4]			Hib	Hib	*Hib*[4]	Hib		Hib			
Pneumococcal[5]			PCV	PCV	PCV	PCV				PCV	PPV
Inactivated Poliovirus			IPV	IPV	IPV		IPV				IPV
Influenza[6]					Influenza (Yearly)						
Measles, Mumps, Rubella[7]						MMR					MMR
Varicella[8]						Varicella					Varicella
Hepatitis A[9]						HepA (2 doses)				HepA Series	
Meningococcal[10]										MPSV4	

Range of recommended ages

Catch-up immunization

Certain high-risk groups

This schedule indicates the recommended ages for routine administration of currently licensed childhood vaccines, as of December 1, 2006, for children through age 6 years. For additional information see **www.cdc.gov/nip/recs/child-schedule.htm**. Any dose not administered at the recommended age should be administered at any subsequent visit when indicated and feasible. 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**.

1. Hepatitis B vaccine (HepB). *(Minimum age: birth)*

At birth:

- Administer monovalent HepB to all newborns prior to hospital discharge.
- If mother is HBsAg-positive, administer HepB and 0.5 mL of hepatitis B immune globulin (HBIG) within 12 hours of birth.
- If mother's HBsAg status is unknown, administer HepB within 12 hours of birth. Determine the HBsAg status as soon as possible and if HBsAg-positive, administer HBIG (no later than age 1 week).
- If mother is HBsAg-negative, the birth dose can only be delayed with physician's order and mothers' negative HBsAg laboratory report documented in the infant's medical record.

Following the birth dose:

- The HepB series should be completed with either monovalent HepB or a combination vaccine containing HepB. The second dose should be administered at age 1–2 months. The final dose should be administered at age ≥24 weeks. Infants born to HBsAg-positive mothers should be tested for HBsAg and antibody to HBsAg after completion of 3 or more doses in a licensed HepB series, at age 9–18 months (generally at the next well-child visit).

4-month dose of HepB:

- It is permissible to administer 4 doses of HepB when combination vaccines are given after the birth dose. If monovalent HepB is used for doses after the birth dose, a dose at age 4 months is not needed.

2. Rotavirus vaccine (Rota). *(Minimum age: 6 weeks)*

- Administer the first dose between 6 and 12 weeks of age. Do not start the series later than age 12 weeks.
- Administer the final dose in the series by 32 weeks of age. Do not administer a dose later than age 32 weeks.
- There are insufficient data on safety and efficacy outside of these age ranges.

3. Diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP). *(Minimum age: 6 weeks)*

- The fourth dose of DTaP may be administered as early as age 12 months, provided 6 months have elapsed since the third dose.
- Administer the final dose in the series at age 4–6 years.

4. *Haemophilus influenzae* type b conjugate vaccine (Hib). *(Minimum age: 6 weeks)*

- If PRP-OMP (PedvaxHIB® or ComVax® [Merck]) is administered at ages 2 and 4 months, a dose at age 6 months is not required.
- TriHiBit® (DTaP/Hib) combination products should not be used for primary immunization but can be used as boosters following any Hib vaccine in ≥12 months olds.

5. Pneumococcal vaccine. *(Minimum age: 6 weeks for Pneumococcal Conjugate Vaccine (PCV); 2 years for Pneumococcal Polysaccharide Vaccine (PPV))*

- Administer PCV at ages 24-59 months in certain high-risk groups. Administer PPV to certain high-risk groups aged ≥2 years. See *MMWR* 2000; 49(RR-9):1-35.

6. Influenza vaccine. *(Minimum age: 6 months for trivalent inactivated influenza vaccine (TIV); 5 years for live, attenuated influenza vaccine (LAIV)*

- All children aged 6–59 months and close contacts of all children aged 0–59 months are recommended to receive influenza vaccine.
- Influenza vaccine is recommended annually for children aged ≥59 months with certain risk factors, healthcare workers, and other persons (including household members) in close contact with persons in groups at high risk. See *MMWR* 2006; 55(RR-10);1-41.
- For healthy persons aged 5–49 years, LAIV may be used as an alternative to TIV.
- Children receiving TIV should receive 0.25 mL if aged 6–35 months or 0.5 mL if aged ≥3 years.
- Children aged ≤9 years who are receiving influenza vaccine for the first time should receive 2 doses (separated by ≥4 weeks for TIV and ≥6 weeks for LAIV).

7. Measles, mumps, and rubella vaccine (MMR). *(Minimum age: 12 months)*

- Administer the second dose of MMR at age 4–6 years. MMR may be administered prior to age 4–6 years, provided ≥4 weeks have elapsed since the first dose and both doses are administered at age ≥12 months.

8. Varicella vaccine. *(Minimum age: 12 months)*

- Administer the second dose of varicella vaccine at age 4–6 years. Varicella vaccine may be administered prior to age 4–6 years, provided that ≥3 months have elapsed since the first dose and both doses are administered at age ≥12 months. If second dose was administered ≥28 days following the first dose, the second dose does not need to be repeated.

9. Hepatitis A vaccine (HepA). *(Minimum age: 12 months)*

- 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.
- Children not fully vaccinated by age 2 years can be vaccinated at subsequent visits.
- HepA is recommended for certain other groups of children including in areas where vaccination programs target older children. See *MMWR* 2006; 55(RR-7):1-23.

10. Meningococcal polysaccharide vaccine (MPSV4). *(Minimum age: 2 years)*

- Administer MPSV4 to children aged 2–10 years with terminal complement deficiencies or anatomic or functional asplenia and certain other high risk groups. See *MMWR* 2005;54 (RR-7):1-21.

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

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A

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

Recommended Immunization Schedule for Ages 7–18 Years UNITED STATES • 2007

Vaccine ▼ / Age ▶	7-10 years	11–12 YEARS	13–14 years	15 years	16–18 years
Tetanus, Diphtheria, Pertussis[1]	see footnote 1	Tdap	Tdap		
Human Papillomavirus[2]	see footnote 2	HPV (3 doses)	HPV Series		
Meningococcal[3]	MPSV4	MCV4	MCV4	MCV4[3]	
Pneumococcal[4]	PPV				
Influenza[5]	Influenza (Yearly)				
Hepatitis A[6]	HepA Series				
Hepatitis B[7]	HepB Series				
Inactivated Poliovirus[8]	IPV Series				
Measles, Mumps, Rubella[9]	MMR Series				
Varicella[10]	Varicella Series				

Range of recommended ages

Catch-up immunization

Certain high-risk groups

This schedule indicates the recommended ages for routine administration of currently licensed childhood vaccines, as of December 1, 2006, for children aged 7–18 years. For additional information see **www.cdc.gov/nip/recs/child-schedule.htm**. Any dose not administered at the recommended earlier age should be administered at any subsequent visit when indicated and feasible. 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**.

FOOTNOTES

1. Tetanus and diphtheria toxoids and acellular pertussis vaccine (Tdap).
(Minimum age: 10 years for BOOSTRIX® and 11 years for ADACEL™)
- Administer at age 11–12 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.

2. Human papillomavirus vaccine (HPV). *(Minimum age: 9 years)*
- Administer the first dose of the HPV vaccine series to females at age 11–12 years.
- Administer the second dose 2 months after the first dose and the third dose 6 months after the first dose.
- Administer the HPV vaccine series to females at age 13–18 years if not previously vaccinated.

3. Meningococcal vaccine. *(Minimum age: 11 years for meningococcal conjugate vaccine (MCV4); 2 years for meningococcal polysaccharide vaccine (MPSV4))*
- Administer MCV4 at age 11–12-years and to previously unvaccinated adolescents at high school entry (~15 years of age).
- Administer MCV4 to previously unvaccinated college freshmen living in dormitories; 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 or MPSV4 for older children.

4. Pneumococcal polysaccharide vaccine (PPV).
(Minimum age: 2 years)
- Administer for certain high-risk groups. See *MMWR* 1997; 46(RR-08); 1–24 and *MMWR* 2000; 49(RR-9):1-35.

5. Influenza vaccine. *(Minimum age: 6 months for trivalent inactivated influenza vaccine (TIV); 5 years for live, attenuated influenza vaccine (LAIV)*
- Influenza vaccine is recommended annually for persons with certain risk factors, healthcare workers, and other persons (including household members) in close contact with persons in groups at high risk. See *MMWR* 2006; 55(RR-10);1-41.
- For healthy persons aged 5–49 years, LAIV may be used as an alternative to TIV.
- Children aged ≤9 years who are receiving influenza vaccine for the first time should receive 2 doses (separated by ≥4 weeks for TIV and ≥6 weeks for LAIV).

6. Hepatitis A vaccine (HepA). *(Minimum age: 12 months)*
- The 2 doses in the series should be administered at least 6 months apart.
- HepA is recommended for certain other groups of children including in areas where vaccination programs target older children. See *MMWR* 2006; 55(RR-7):1-23.

7. Hepatitis B vaccine (HepB). *(Minimum age: birth)*
- Administer the 3-dose series to those who were not previously vaccinated.
- A 2-dose series of Recombivax HB® is licensed for 11–15 year olds.

8. Inactivated poliovirus vaccine (IPV). *(Minimum age: 6 weeks)*
- 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.

9. Measles, mumps, and rubella vaccine (MMR).
(Minimum age: 12 months)
- If not previously vaccinated, administer 2 doses of MMR during any visit with ≥4 weeks between the doses.

10. Varicella vaccine. *(Minimum age: 12 months)*
- Administer 2 doses of varicella vaccine to persons without evidence of immunity.
- Administer 2 doses of varicella vaccine to persons aged <13 years at least 3 months apart. Do not repeat the second dose, if administered ≥28 days following the first dose.
- Administer 2 doses of varicella vaccine to persons aged ≥13 years at least 4 weeks apart.

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

UNITED STATES • 2007

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 table appropriate for the child's age.

CATCH-UP SCHEDULE FOR AGES 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
Hepatitis B[1]	Birth	4 weeks	8 weeks (and 16 weeks after first dose)		
Rotavirus[2]	6 wks	4 weeks	4 weeks		
Diphtheria, Tetanus, Pertussis[3]	6 wks	4 weeks	4 weeks	6 months	6 months[3]
Haemophilus influenzae type b[4]	6 wks	4 weeks if first dose 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[4] if current age <12 months 8 weeks (as final dose)[4] if current age ≥12 months and second dose given at age <15 months No further doses needed if previous dose given at age ≥15 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	
Pneumococcal[5]	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	
Inactivated Poliovirus[6]	6 wks	4 weeks	4 weeks	4 weeks[6]	
Measles, Mumps, Rubella[7]	12 mos	4 weeks			
Varicella[8]	12 mos	3 months			
Hepatitis A[9]	12 mos	6 months			

CATCH-UP SCHEDULE FOR AGES 7–18 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
Tetanus, Diphtheria/ Tetanus, Diphtheria, Pertussis[10]	7 yrs[10]	4 weeks	8 weeks if first dose given at age <12 months 6 months if first dose given at age ≥12 months	6 months if first dose given at age <12 months	
Human Papillomavirus[11]	9 yrs	4 weeks	12 weeks		
Hepatitis A[9]	12 mos	6 months			
Hepatitis B[1]	Birth	4 weeks	8 weeks (and 16 weeks after first dose)		
Inactivated Poliovirus[6]	6 wks	4 weeks	4 weeks	4 weeks[6]	
Measles, Mumps, Rubella[7]	12 mos	4 weeks			
Varicella[8]	12 mos	4 weeks if first dose given at age ≥13 years 3 months if first dose given at age <13 years			

1. Hepatitis B vaccine (HepB). *(Minimum age: birth)*
- Administer the 3-dose series to those who were not previously vaccinated.
- A 2-dose series of Recombivax HB® is licensed for 11–15 year olds.

2. Rotavirus vaccine (Rota). *(Minimum age: 6 weeks)*
- Do not start the series later than age 12 weeks.
- Administer the final dose in the series by 32 weeks of age. Do not administer a dose later than age 32 weeks.
- There are insufficient data on safety and efficacy outside of these age ranges.

3. Diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP). *(Minimum age: 6 weeks)*
- The fifth dose is not necessary if the fourth dose was administered at age ≥4 years.
- DTaP is not indicated for persons aged ≥7 years.

4. *Haemophilus influenzae* type b conjugate vaccine (Hib). *(Minimum age: 6 weeks)*
- Vaccine is not generally recommended for children aged ≥5 years.
- 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.
- If first dose given at age 7–11 months, give 2 doses separated by 4 weeks plus a booster at age 12–15 months.

5. Pneumococcal conjugate vaccine (PCV). *(Minimum age: 6 weeks)*
- Vaccine is not generally recommended for children aged ≥5 years.

6. Inactivated poliovirus vaccine (IPV). *(Minimum age: 6 weeks)*
- 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.

7. Measles, mumps, and rubella vaccine (MMR). *(Minimum age: 12 months)*
- The second dose of MMR is recommended routinely at age 4–6 years but may be administered earlier if desired.
- If not previously vaccinated, administer 2 doses of MMR during any visit with ≥4 weeks between the doses.

8. Varicella vaccine. *(Minimum age: 12 months)*
- The second dose of varicella vaccine is recommended routinely at age 4–6 years but may be administered earlier if desired.
- Do not repeat the second dose in persons aged <13 years, if administered ≥28 days following the first dose.

9. Hepatitis A vaccine (HepA). *(Minimum age: 12 months)*
- HepA is recommended for certain groups of children including in areas where vaccination programs target older children. See *MMWR* 2006; SS (RR-7) 1-23.

10. Tetanus and diphtheria toxoids vaccine (Td) and tetanus and diphtheria toxoids and acellular pertussis vaccine (Tdap). *(Minimum ages: 7 years for Td, 10 years for BOOSTRIX®, and 11 years for ADACEL™)*
- Tdap should be substituted for a single dose of Td in the primary catch-up series or as a booster if age-appropriate; use Td for other doses.
- A five-year interval from the last Td dose is encouraged when Tdap is used as a booster dose. A booster (4th) dose is needed if any of the previous doses were administered at age <12 months. Refer to ACIP recommendations for further information. See *MMWR* 2006; SS (RR-3) L34.

11. Human papillomavirus vaccine (HPV). *(Minimum age: 9 years)*
- Administer the HPV vaccine series to females at age 13–18 years if not previously vaccinated.

For information on reporting reactions following immunization, 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 including precautions and contraindications for immunization, visit the National Center for Immunization and Respiratory Diseases at www.cdc.gov/ncird or contact 800-CDC-INFO (800-232-4636).

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Recommended Adult Immunization Schedule, by Vaccine and Age Group
UNITED STATES • OCTOBER 2006–SEPTEMBER 2007

Vaccine ▼ / Age group ▶	19–49 years	50–64 years	≥65 years
Tetanus, diphtheria, pertussis (Td/Tdap)[1,*]	1-dose Td booster every 10 yrs; Substitute 1 dose of Tdap for Td		
Human papillomavirus (HPV)[2]	3 doses (females)		
Measles, mumps, rubella (MMR)[3,*]	1 or 2 doses	1 dose	
Varicella[4,*]	2 doses (0, 4–8 wks)	2 doses (0, 4–8 wks)	
Influenza[5,*]	1 dose annually	1 dose annually	
Pneumococcal (polysaccharide)[6,7]	1–2 doses		1 dose
Hepatitis A[8,*]	2 doses (0, 6–12 mos, or 0, 6–18 mos)		
Hepatitis B[9,*]	3 doses (0, 1–2, 4–6 mos)		
Meningococcal[10]	1 or more doses		

*Covered by the Vaccine Injury Compensation Program. NOTE: These recommendations must be read with the footnotes (see reverse).

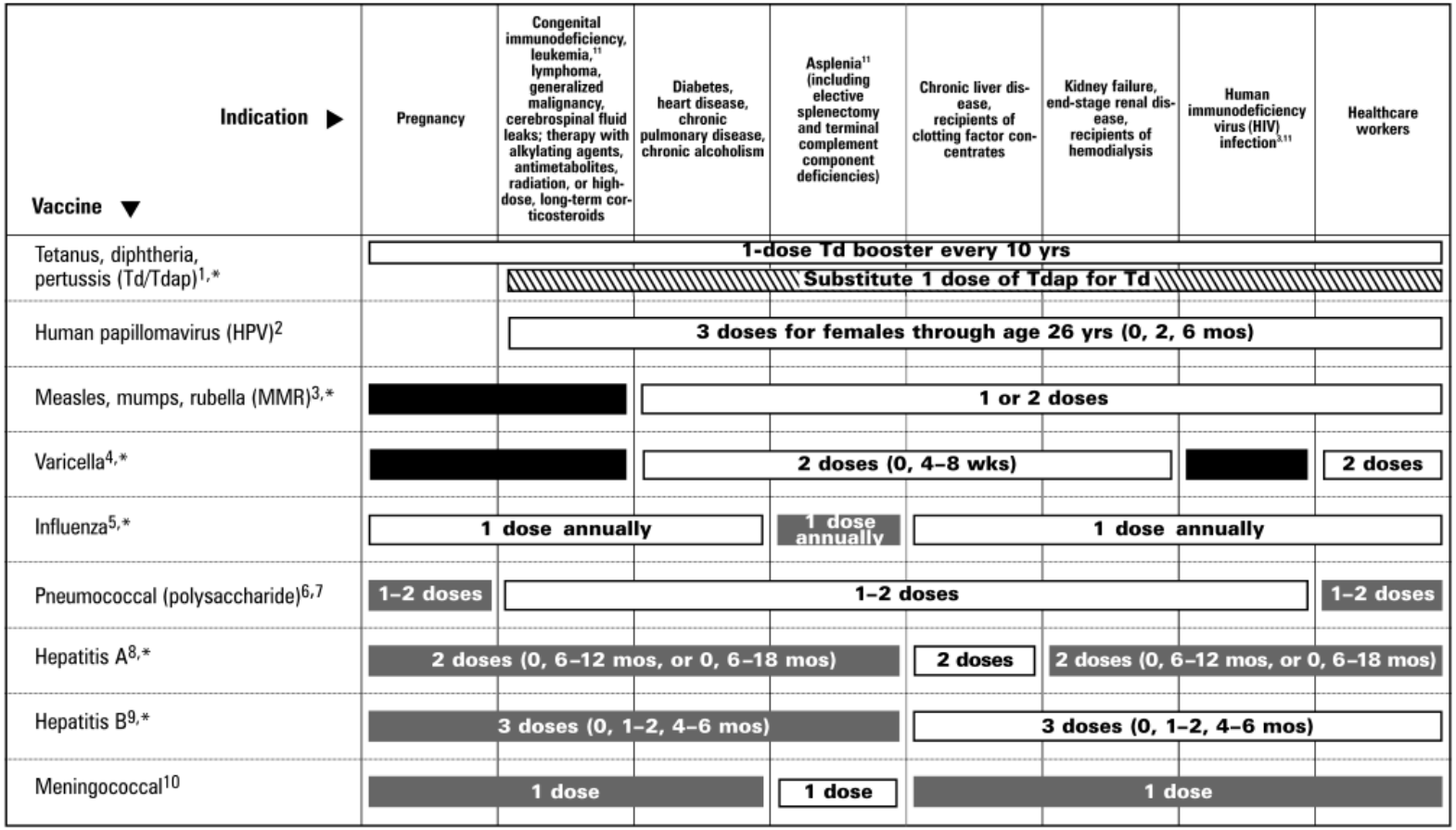
This schedule indicates the recommended age groups and medical indications for routine administration of currently licensed vaccines for persons aged ≥19 years, as of October 1, 2006. Licensed combination vaccines may be used whenever any components of the combination are indicated and when the vaccine's other components are not contraindicated. For detailed recommendations on all vaccines, including those used primarily for travelers or that are issued during the year, consult the manufacturers' package inserts and the complete statements from the Advisory Committee on Immunization Practices (www.cdc.gov/nip/publications/acip-list.htm).

Report all clinically significant postvaccination reactions to the Vaccine Adverse Event Reporting System (VAERS). Reporting forms and instructions on filing a VAERS report are available at www.vaers.hhs.gov or by telephone, 800-822-7967.

Information on how to file a Vaccine Injury Compensation Program claim is available at www.hrsa.gov/vaccinecompensation or by telephone, 800-338-2382. To file a claim for vaccine injury, contact the U.S. Court of Federal Claims, 717 Madison Place, N.W., Washington, D.C. 20005; telephone, 202-357-6400.

Additional information about the vaccines in this schedule and contraindications for vaccination is also available at www.cdc.gov/nip or from the CDC-INFO Contact Center at 800-CDC-INFO (800-232-4636) in English and Spanish, 24 hours a day, 7 days a week.

Recommended Adult Immunization Schedule, by Vaccine and Medical and Other Indications
UNITED STATES • OCTOBER 2006–SEPTEMBER 2007



*Covered by the Vaccine Injury Compensation Program. NOTE: These recommendations must be read with the footnotes (see reverse).

For all persons in this category who meet the age requirements and who lack evidence of immunity (e.g., lack documentation of vaccination or have no evidence of prior infection)

Recommended if some other risk factor is present (e.g., on the basis of medical, occupational, lifestyle, or other indications)

Contraindicated

Approved by
the Advisory Committee on Immunization Practices,
the American College of Obstetricians and Gynecologists,
the American Academy of Family Physicians,
and the American College of Physicians

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

Footnotes
Recommended Adult Immunization Schedule • UNITED STATES, OCTOBER 2006–SEPTEMBER 2007

1. **Tetanus, diphtheria, and acellular pertussis (Td/Tdap) vaccination.** Adults with uncertain histories of a complete primary vaccination series with diphtheria and tetanus toxoid–containing vaccines should begin or complete a primary vaccination series. 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 a booster dose to adults who have completed a primary series and if the last vaccination was received ≥10 years previously. Tdap or tetanus and diphtheria (Td) vaccine may be used; Tdap should replace a single dose of Td for adults aged <65 years who have not previously received a dose of Tdap (either in the primary series, as a booster, or for wound management). Only one of two Tdap products (Adacel® [sanofi pasteur]) is licensed for use in adults. If the person is pregnant and received the last Td vaccination ≥10 years previously, administer Td during the second or third trimester; if the person received the last Td vaccination in <10 years, administer Tdap during the immediate postpartum period. A one-time administration of 1 dose of Tdap with an interval as short as 2 years from a previous Td vaccination is recommended for postpartum women, close contacts of infants aged <12 months, and all healthcare workers with direct patient contact. In certain situations, Td can be deferred during pregnancy and Tdap substituted in the immediate postpartum period, or Tdap can be given instead of Td to a pregnant woman after an informed discussion with the woman (see www.cdc.gov/nip/publications/acip-list.htm). Consult the ACIP statement for recommendations for administering Td as prophylaxis in wound management (www.cdc.gov/mmwr/preview/mmwrhtml/00041645.htm).

2. **Human papillomavirus (HPV) vaccination.** HPV vaccination is recommended for all women aged ≤26 years who have not completed the vaccine series. Ideally, vaccine should be administered before potential exposure to HPV through sexual activity; however, women who are sexually active should still be vaccinated. Sexually active women who have not been infected with any of the HPV vaccine types receive the full benefit of the vaccination. Vaccination is less beneficial for women who have already been infected with one or more of the four HPV vaccine types. A complete series consists of 3 doses. The second dose should be administered 2 months after the first dose; the third dose should be administered 6 months after the first dose. Vaccination is not recommended during pregnancy. If a woman is found to be pregnant after initiating the vaccination series, the remainder of the 3-dose regimen should be delayed until after completion of the pregnancy.

3. **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) have been recently exposed to measles or in an outbreak setting; 2) have been previously vaccinated with killed measles vaccine; 3) have been vaccinated with an unknown type of measles vaccine during 1963–1967; 4) are students in postsecondary educational institutions; 5) work in ahealthcare facility; or 6) plan to travel internationally. Withhold MMR or other measles-containing vaccines from HIV-infected persons with severe immunosuppression.

   Mumps component: adults born before 1957 can generally be considered immune to mumps. Adults born during or after 1957 should receive 1 dose of MMR unless they have a medical contraindication, history of mumps based on healthcare provider diagnosis, or laboratory evidence of immunity. A second dose of MMR is recommended for adults who 1) are in an age group that is affected during a mumps outbreak; 2) are students in postsecondary educational institutions; 3) work in a healthcare facility; or 4) plan to travel internationally. For unvaccinated healthcare workers born before 1957 who do not have other evidence of mumps immunity, consider giving 1 dose on a routine basis and strongly consider giving a second dose during an outbreak. *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 who might become pregnant within 4 weeks of receiving 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.

4. **Varicella vaccination.** All adults without evidence of immunity to varicella should receive 2 doses of varicella vaccine. Special consideration should be given to those who 1) have close contact with persons at high risk for severe disease (e.g., 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) documentation of 2 doses of varicella vaccine at least 4 weeks apart; 2) U.S.-born before 1980 (although for healthcare workers and pregnant women, birth before 1980 should not be considered evidence of immunity); 3) history of varicella based on diagnosis or verification of varicella by a healthcare provider (for a patient reporting a history of or presenting with an atypical case, a mild case, or both, 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 or laboratory confirmation of disease. 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 administered 4–8 weeks after dose 1.

5. **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 HIV); any condition that compromises respiratory function or the handling of respiratory secretions or that can increase the risk of aspiration (e.g., cognitive dysfunction, spinal cord injury, or seizure disorder or other neuromuscular disorder); and pregnancy during the influenza season. No data exist on the risk for severe or complicated influenza disease among persons with asplenia; however, influenza is a risk factor for secondary bacterial infections that can cause severe disease among persons with asplenia. *Occupational indications:* 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 (e.g., in-home household contacts and caregivers of children aged 0–59 months, or persons of all ages with high-risk conditions); and anyone who would like to be vaccinated. Healthy, nonpregnant persons aged 5–49 years without high-risk medical conditions who are not contacts of severely immunocompromised persons in special care units can receive either intranasally administered influenza vaccine (FluMist®) or inactivated vaccine. Other persons should receive the inactivated vaccine.

6. **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, or 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 and residents of nursing homes or other long-term–care facilities.

7. **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, or 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.

8. **Hepatitis A vaccination.** *Medical indications:* persons with chronic liver disease and persons who receive clotting factor concentrates. *Behavioral indications:* men who have sex with men and persons who use illegal drugs. *Occupational indications:* persons working with hepatitis A virus (HAV)–infected primates or with HAV in a research laboratory setting. *Other indications:* persons traveling to or working in countries that have high or intermediate endemicity of hepatitis A (a list of countries is available at www.cdc.gov/travel/diseases.htm) and any person who would like to obtain immunity. Current vaccines should be administered in a 2-dose schedule 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.

9. **Hepatitis B vaccination.** *Medical indications:* persons with end-stage renal disease, including patients receiving hemodialysis; persons seeking evaluation or treatment for a sexually transmitted disease (STD); persons with HIV infection; persons with chronic liver disease; and persons who receive clotting factor concentrates. *Occupational indications:* healthcare workers and public-safety workers who are exposed to blood or other potentially infectious body fluids. *Behavioral indications:* sexually active persons who are not in a long-term, mutually monogamous relationship (i.e., persons with >1 sex partner during the previous 6 months); current or recent injection-drug users; and men who have sex with men. *Other indications:* household contacts and sex partners of persons with chronic hepatitis B virus (HBV) infection; clients and staff members of institutions for persons with developmental disabilities; all clients of STD clinics; international travelers to countries with high or intermediate prevalence of chronic HBV infection (a list of countries is available at www.cdc.gov/travel/diseases.htm); and any adult seeking protection from HBV infection. Settings where hepatitis B vaccination is recommended for all adults: STD treatment facilities; HIV testing and treatment facilities; facilities providing drug-abuse treatment and prevention services; healthcare settings providing services for injection-drug users or men who have sex with men; correctional facilities; end-stage renal disease programs and facilities for chronic hemodialysis patients; and institutions and nonresidential daycare facilities for persons with developmental disabilities. *Special formulation indications:* for adult patients receiving hemodialysis and other immunocompromised adults, 1 dose of 40 μg/mL (Recombivax HB®) or 2 doses of 20 μg/mL (Engerix-B®).

10. **Meningococcal vaccination.** *Medical indications:* adults with anatomic or functional asplenia, or terminal complement component deficiencies. *Other indications:* first-year college students living in dormitories; microbiologists who are routinely exposed to isolates of *Neisseria meningitidis*; military recruits; and persons who travel to or live in countries in which meningococcal disease is hyperendemic or epidemic (e.g., the "meningitis belt" of sub-Saharan Africa during the dry season [December–June]), particularly if their contact with local populations will be prolonged. Vaccination is required by the government of Saudi Arabia for all travelers to Mecca during the annual Hajj. Meningococcal conjugate vaccine is preferred for adults with any of the preceding indications who are aged ≤55 years, although meningococcal polysaccharide vaccine (MPSV4) is an acceptable alternative. Revaccination after 5 years might 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).

11. **Selected conditions for which *Haemophilus influenzae* type b (Hib) vaccine may be used.** Hib 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 who have had splenectomies; administering vaccine to these patients is not contraindicated.

Use of trade names and commercial sources is for identification only and does not imply endorsement by the U.S. Department of Health and Human Services.

Appendix A

Recommended and Minimum Ages and Intervals Between Doses of Routinely Recommended Vaccines[1]

Vaccine and dose number	Recommended age for this dose	Minimum age for this dose	Recommended interval to next dose	Minimum interval to next dose
Hepatitis B (HepB)-1[2]	Birth	Birth	1-4 months	4 weeks
HepB-2	1-2 months	4 weeks	2-17 months	8 weeks
HepB-3[3]	6-18 months	24 weeks	–	–
Diphtheria-tetanus-acellular pertussis (DTaP)-1[2]	2 months	6 weeks	2 months	4 weeks
DTaP-2	4 months	10 weeks	2 months	4 weeks
DTaP-3	6 months	14 weeks	6-12 months[4]	6 months[4,5]
DTaP-4	15-18 months	12 months	3 years	6 months[4]
DTaP-5	4-6 years	4 years	–	–
Haemophilus influenzae type b (Hib)-1[2,6]	2 months	6 weeks	2 months	4 weeks
Hib-2	4 months	10 weeks	2 months	4 weeks
Hib-3[7]	6 months	14 weeks	6-9 months[4]	8 weeks
Hib-4	12-15 months	12 months	–	–
Inactivated poliovirus (IPV)-1[2]	2 months	6 weeks	2 months	4 weeks
IPV-2	4 months	10 weeks	2-14 months	4 weeks
IPV-3	6-18 months	14 weeks	3-5 years	4 weeks
IPV-4	4-6 years	18 weeks	–	–
Pneumococcal conjugate (PCV)-1[6]	2 months	6 weeks	2 months	4 weeks
PCV-2	4 months	10 weeks	2 months	4 weeks
PCV-3	6 months	14 weeks	6 months	8 weeks
PCV-4	12-15 months	12 months	–	–
Measles-mumps-rubella (MMR)-1[8]	12-15 months	12 months	3-5 years	4 weeks
MMR-2[8]	4-6 years	13 months	–	–
Varicella (Var)-1[8]	12-15 months	12 months	3-5 years	12 weeks [9]
Var-2[8]	4-6 years	15 months	–	–
Hepatitis A (HepA)-1[2]	12-23 months	12 months	6-18 months[4]	6 months[4]
HepA-2	18-41 months	18 months	–	–
Influenza, Inactivated (TIV)[10]	6-59 months	6 months[11]	1 month	4 weeks
Influenza, Live attenuated (LAIV)[10]	–	5 years	6-10 weeks	6 weeks
Meningococcal Conjugate (MCV)	11-12 years	11 years	–	–
Meningococcal Polysaccharide (MPSV)-1	–	2 years	5 years[12]	5 years[12]
MPSV-2[13]	–	7 years	–	–
Tetanus-diphtheria (Td)	11-12 years	7 years	10 years	5 years
Tetanus-diphtheria-acellular pertussis (Tdap)[14]	≥11 years	10 years	–	–
Pneumococcal polysaccharide (PPV)-1	–	2 years	5 years	5 years
PPV-2[15]	–	7 years	–	–

Vaccine and dose number	Recommended age for this dose	Minimum age for this dose	Recommended interval to next dose	Minimum interval to next dose
Human papillomavirus (HPV)-1[16]	11-12 years	9 years	2 months	4 weeks
HPV-2	11-12 years (+2 months)	109 months	4 months	12 weeks
HPV-3	11-12 years (+6 months)	112 months	–	–
Rotavirus (RV)-1[17]	2 months	6 weeks	2 months	4 weeks
RV-2	4 months	10 weeks	2 months	4 weeks
RV-3	6 months	14 weeks	–	–
Zoster[18]	60 years	60 years	–	–

1 Use of licensed combination vaccines is preferred over separate injections of their equivalent component vaccines. (CDC. Combination vaccines for childhood immunization: recommendations of the Advisory Committee on Immunization Practices [ACIP], the American Academy of Pediatrics [AAP], and the American Academy of Family Physicians [AAFP]. *MMWR* 1999;48[No. RR-5]). When administering combination vaccines, the minimum age for administration is the oldest age for any of the individual components; the minimum interval between doses is equal to the greatest interval of any of the individual components.

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

3 HepB-3 should be administered at least 8 weeks after HepB-2 and at least 16 weeks after HepB-1, and it should not be administered before age 24 weeks.

4 Calendar months.

5 The minimum recommended interval between DTaP-3 and DTaP-4 is 6 months. However, DTaP-4 need not be repeated if administered at least 4 months after DTaP-3.

6 For Hib and PCV, children receiving the first dose of vaccine at age 7 months of age or older require fewer doses to complete the series (CDC. Recommended childhood and adolescent immunization schedule – United States, 2006. *MMWR* 2005; 54 [Nos. 51 & 52]:Q1-Q4).

7 If PRP-OMP (Pedvax-Hib®, Merck Vaccine Division), was administered at 2 and 4 months of age a dose at 6 months of age is not required.

8 Combination measles-mumps-rubella-varicella (MMRV) vaccine can be used for children 12 months through 12 years of age. Also see footnote 9.

9 The minimum interval from Var-1 to Var-2 for persons beginning the series at 13 years or older is 4 weeks.

10 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.

11 The minimum age for inactivated influenza vaccine varies by vaccine manufacturer. Only Fluzone (manufactured by sanofi pasteur) is approved for children 6-35 months of age. The minimum age for Fluvirin (manufactured by Novartis) is 4 years. For Fluarix and FluLaval (manufactured by GlaxoSmithKline), the minimum age is 18 years.

12 Some experts recommend a second dose of MPSV 3 years after the first dose for people at increased risk for meningococcal disease.

13 A second dose of meningococcal vaccine is recommended for people previously vaccinated with MPSV who remain at high risk for meningococcal disease. MCV is preferred when revaccinating persons aged 11-55 years, but a second dose of MPSV is acceptable. (CDC. Prevention and Control of Meningococcal Disease Recommendations of the Advisory Committee on Immunization Practices [ACIP]. *MMWR* 2005; 54: No. RR-7.)

14 Only one dose of Tdap is recommended. Subsequent doses should be administered as Td. If vaccination to prevent tetanus and/or diphtheria disease is required for children 7 through 9 years of age, Td should be administered (minimum age for Td is 7 years). For one brand of Tdap the minimum age is 11 years. The preferred interval between Tdap and a previous dose of Td is 5 years. In persons who have received a primary series of tetanus-toxoid containing vaccine, for management of a tetanus-prone wound, the minimum interval after a previous dose of any tetanus-containing vaccine is 5 years.

15 A second dose of 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. (CDC. Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunization Practices [ACIP]. *MMWR* 1997;46[No. RR-8]).

16 HPV is approved only for females 9-26 years of age.

17 The first dose of RV must be administered at 6-12 weeks of age. The vaccine series should not be started at 13 weeks of age or older. RV should not be administered to children 33 weeks of age or older regardless of the number of doses received between 6 and 32 weeks of age.

18 Herpes zoster vaccine is approved as a single dose for persons 60 years and older with a history of varicella.

Adapted from Table 1, ACIP General Recommendations on Immunization: *MMWR* 2006;55(No. RR-15) December **2006**

Summary of Recommendations for Childhood and Adolescent Immunization (Page 1 of 3)

Adapted from the recommendations of the Advisory Committee on Immunization Practices (ACIP)* by the Immunization Action Coalition, November 2006

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 ages 0 through 18yrs. • 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 (ages 2m, 4m, 12–15m) or Pediarix (ages 2m, 4m, 6m), which may result in giving a total of 4 doses of hepatitis B vaccine. • **If mother is HBsAg-positive:** give the newborn HBIG + dose #1 within 12hrs of birth; complete series at age 6m or, if using Comvax, at 12–15m. • **If mother's HBsAg status is unknown:** give the newborn dose #1 within 12hrs of birth. If mother is subsequently found to be HBsAg positive, give infant HBIG within 7d of birth and follow the schedule for infants born to HBsAg-positive mothers.	• Do not restart series, no matter how long since previous dose. • 3-dose series can be started at any age. • Minimum spacing between doses: 4wks between #1 and #2, 8wks between #2 and #3, and at least 16wks between #1 and #3 (e.g., 0-, 2-, 4m; 0-, 1-, 4m). **Special Notes on Hepatitis B Vaccine (HepB)** **Dosing of HepB:** Vaccine brands are interchangeable. For persons ages 0 through 19yrs, give 0.5 mL of either Engerix-B or Recombivax HB. **Alternative dosing schedule for unvaccinated adolescents ages 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 preterm infants:** Consult ACIP hepatitis B recommendations (*MMWR* 2005; 54 [RR-16]).	**Contraindication:** Previous anaphylaxis to this vaccine or to any of its components. **Precaution** Moderate or severe acute illness.
DTaP, DT (Diphtheria, tetanus, acellular pertussis) *Give IM*	• Give to children at ages 2m, 4m, 6m, 15–18m, 4–6yrs. • May give dose #1 as early as age 6wks. • May give #4 as early as age 12m if 6m have elapsed since #3 and the child is unlikely to return at age 15–18m. • Do not give DTaP/DT to children age 7yrs and older. • If possible, use the same DTaP product for all doses.	• #2 and #3 may be given 4wks after previous dose. • #4 may be given 6m after #3. • If #4 is given before 4th birthday, wait at least 6m for #5 (age 4–6yrs). • If #4 is given after 4th birthday, #5 is not needed.	**Contraindications** • Previous anaphylaxis to this vaccine or to any of its components. • For DTaP/Tdap only: encephalopathy within 7d after DTP/DTaP. **Precautions** • Moderate or severe acute illness. • Guillain-Barré syndrome within 6wks after previous dose of tetanus toxoid-containing vaccine. • For DTaP only: Any of these occurrences following a previous dose of DTP/DTaP: 1) temperature of 105°F (40.5°C) or higher within 48hrs; 2) continuous crying for 3hrs or more within 48hrs; 3) collapse or shock-like state within 48hrs; 4) convulsion with or without fever within 3d. • For DTaP/Tdap only: Unstable neurologic disorder. **Note:** Use of Td or Tdap is not contraindicated in pregnancy. At the provider's discretion, either vaccine may be administered during the 2nd or 3rd trimester.
Td, Tdap (Tetanus, diphtheria, acellular pertussis) *Give IM*	• Give Tdap booster dose to adolescents age 11–12yrs if 5yrs have elapsed since last dose DTaP/DTP; boost every 10yrs with Td. • Give 1-time Tdap to all adolescents who have not received previous Tdap. Special efforts should be made to give Tdap to persons age 11yrs and older who are - in contact with infants younger than age 12m. - healthcare workers with direct patient contact. • In pregnancy, when indicated, give Td or Tdap in 2nd or 3rd trimester. If not administered during pregnancy, give Tdap in immediate postpartum period.	• If never vaccinated with tetanus- and diphtheria-containing vaccine: give Td dose #1 now, dose #2 4wks later, and dose #3 6m after #2, then give booster every 10yrs. A 1-time Tdap may be substituted for any dose in the series. • Intervals of 2yrs or less between Td and Tdap may be used if needed.	
Polio (IPV) *Give SC or IM*	• Give to children at ages 2m, 4m, 6–18m, 4–6yrs. • May give #1 as early as age 6wks. • 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 anaphylaxis to this vaccine or to any of its components. **Precautions** • Moderate or severe acute illness. • Pregnancy.
Human Papillomavirus (HPV) *Give IM*	• Give 3-dose series to girls at age 11–12yrs on a 0, 2, 6m schedule. • May be given as early as age 9yrs. • Vaccinate all older females (through age 26yrs) not previously vaccinated.	• Dose #2 may be given 4wks after dose #1. • Dose #3 may be given 12wks after dose #2.	**Contraindication** Previous anaphylaxis to this vaccine or to any of its components. **Precautions** • Moderate or severe acute illness. • Pregnancy.

*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 periodically. 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 Center for Immunization and Respiratory Diseases for his assistance. For more information, contact IAC at 1573 Selby Avenue, St. Paul, MN 55104, (651) 647-9009, or email admin@immunize.org.

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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 dose #1 at age 12–15m. • Give dose #2 at age 4–6yrs. Dose #2 may be given earlier if at least 3m since dose #1. • Give a routine second dose to all older children and adolescents with history of only 1 dose. • MMRV may be used in children 12m through 12yrs.	• If younger than age 13yrs, space dose #1 and #2 at least 3m apart. If age 13yrs or older, space 4–8wks apart. • May use as postexposure prophylaxis if given within 3–5d. • If Var and either MMR, LAIV, and/or yellow fever vaccine are not given on the same day, space them at least 28d apart.	**Contraindications** • Previous anaphylaxis to this vaccine or to any of its components. • Pregnancy or possibility of pregnancy within 4wks. • Children 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.
MMR (Measles, mumps, rubella) *Give SC*	• Give dose #1 at age 12–15m. • Give dose #2 at age 4–6yrs. Dose #2 may be given earlier if at least 4wks since dose #1. • If a dose was given before age12m, it doesn't count as the first dose, so give #1 at age 12–15m with a minimum interval of 4wks between the invalid dose and dose #1. • MMRV may be used in children 12m through 12yrs.	• If MMR and either Var, LAIV, and/or yellow fever vaccine are not given on the same day, space them at least 28d apart. • When using MMR (not MMRV) for both doses, minimum interval is 4wks.	**Contraindications** • Previous anaphylaxis to this vaccine or to any of its components. • Pregnancy or possibility of pregnancy within 4wks. • Severe immunodeficiency (e.g., hematologic and solid tumors; congenital immunodeficiency; long-term immunosuppressive therapy, or severely symptomatic HIV). **Precautions** • Moderate or severe acute illness. • 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 (tuberculosis skin 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* Live attenuated influenza vaccine (LAIV) *Give intranasally*	• On an annual basis, vaccinate all children ages 6–59m, as well as all siblings and household contacts of children ages 0–59m. • Vaccinate persons 5yrs and older who - have a risk factor (e.g., pregnancy, heart disease, lung disease, diabetes, renal dysfunction, hemoglobinopathy, immunosuppression, on long-term aspirin therapy, or have a condition that compromises respiratory function or the handling of respiratory secretions or that can increase the risk of aspiration) or live in a chronic-care facility. - live or work with at-risk people as listed above. • Vaccinate any person wishing to reduce the likelihood of becoming ill with influenza. • LAIV may be given to healthy, non-pregnant persons ages 5–49yrs. • Give 2 doses to first-time vaccinees ages 6m through 8yrs. For TIV, space 4wks apart; for LAIV, space 6wks apart (no younger than age 5yrs). • For TIV, give 0.25 mL dose to children ages 6–35m and 0.5 mL dose if age 3yrs and older.		**Contraindications** • Previous anaphylaxis to this vaccine, to any of its components, or to eggs. • For LAIV only: Pregnancy, asthma, reactive 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. **Precautions** • Moderate or severe acute illness. • For TIV only: History of Guillain-Barré syndrome within 6wks of previous TIV.
Rotavirus (Rota) *Give orally*	• Give a 3-dose series at ages 2m, 4m, 6m. • May give dose #1 as early as age 6wks. • Give dose #3 no later than age 32wks.	• Do not begin series in infants older than age 12wks. • Dose #2 and #3 may be given 4wks after previous dose.	**Contraindication** Previous anaphylaxis to this vaccine or to any of its components. **Precautions** • Moderate or severe acute illness. • Altered immunocompetence. • Moderate to severe acute gastroenteritis or chronic gastrointestinal disease. • History of intussusception.

Summary of Recommendations for Childhood and Adolescent Immunization

Vaccine name and route	Schedule for routine vaccination and other guidelines (any vaccine can be given with another)	Schedule for catch-up vaccination and other related issues	Contraindications and precautions (mild illness is not a contraindication)
Hib (*Haemophilus influenzae* type b) *Give IM*	• HibTITER (HbOC) and 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 age 6wks. • The last dose (booster dose) is given no earlier than age 12m and a minimum of 8wks after the previous dose. • Hib vaccines are interchangeable; however, if different brands of Hib vaccines are administered, 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 age 15m 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 boost at 12–15m (wait at least 8wks after dose #2). **PedvaxHIB and Comvax:** • #2 may be given 4wks after dose #1.	**Contraindication** Previous anaphylaxis to this vaccine or to any of its components. **Precaution** Moderate or severe acute illness.
Pneumo. conjugate (PCV) *Give IM*	• Give at ages 2m, 4m, 6m, 12–15m. • Dose #1 may be given as early as age 6wks. • Give 1 dose to unvaccinated healthy children ages 24–59m. • Give 2 doses at least 8wks apart to unvaccinated high-risk** children ages 24–59m. • PCV is not routinely given to children age 5yrs and older. ****High-risk:** Those with sickle cell disease; anatomic/functional asplenia; chronic cardiac, pulmonary, or renal disease; diabetes; cerebrospinal fluid leaks; HIV infection; immunosuppression; or who have or will have a cochlear implant.	• For ages 7–11m: If history of 0–2 doses, give additional doses 4wks apart with no more than 3 total doses by age 12m; then give booster 8wks later. • For ages 12–23m: If 0–1 dose before age 12m, give 2 doses at least 8wks apart. If 2–3 doses before age 12m, give 1 dose at least 8wks after previous dose. • For ages 24–59m: If patient has had no previous doses, or has a history of 1–3 doses given before age 12m but no booster dose, or has a history of only 1 dose given at 12–23m, give 1 dose now.	**Contraindication** Previous anaphylaxis to this vaccine or to any of its components. **Precaution** Moderate or severe acute illness.
Pneumo. polysacch. (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 who are immunocompromised or have sickle cell disease or functional or anatomic asplenia, give a 2nd dose of PPV 3–5yrs after previous PPV (consult ACIP PPV recommendations [*MMWR* 1997;46 [RR-8] for details*).		**Contraindication** Previous anaphylaxis to this vaccine or to any of its components. **Precaution** Moderate or severe acute illness.
Hepatitis A *Give IM*	• Give 2 doses to all children at age 1yr (12–23m) spaced 6m apart. • Vaccinate all children and adolescents age 2 years and older who - Live in a state, county, or community with a routine vaccination program already in place for children ages 2yrs and older. - Travel anywhere except U.S., W. Europe, N. Zealand, Australia, Canada, or Japan. - Wish to be protected from HAV infection. - Have chronic liver disease, clotting factor disorder, or are MSM adolescents.	• Minimum interval between doses is 6m. • Consider routine vaccination of children ages 2yrs and older in areas with no existing program.	**Contraindication** Previous anaphylaxis 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-time dose of MCV4 to adolescents ages 11–12yrs, 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). **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 anaphylaxis 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, September 2006

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 (December–March). • All healthcare workers and other persons who provide direct care to at-risk people. • Household contacts and out-of-home caregivers of children ages 0–59m. • Travelers at risk for complications of influenza who go to areas where influenza activity exists or who may be among people from areas of the world where there is current influenza activity (e.g., on organized tours). • 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 in the fall or winter. • October and November are the ideal months to give TIV. • LAIV may be given as early as August. • Continue to give TIV and LAIV through the influenza season from December through March (including when influenza activity is present in the community) and at other times when the risk of influenza exists.	**Contraindication** Previous anaphylactic reaction to this vaccine, to any of its components, or to eggs. **Precautions** • Moderate or severe acute illness. • History of Guillain-Barré syndrome within 6wks of previous TIV.
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 (except persons in close contact with severely immunosuppressed persons). - Household contacts and out-of-home caregivers of children ages 0–59m. - 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 (PPV) *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); 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.

*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.

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www.immunize.org/catg.d/p2011b.pdf • Item #P2011 (9/06)

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; any adult wishing to obtain immunity. • 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.
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; injecting and non-injecting 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 doses #1 and #2 is 6m. • If dose #2 is delayed, do not repeat dose #1. Just give dose #2.	**Contraindication** Previous anaphylactic reaction to this vaccine or to any of its components. **Precautions** • Moderate or severe acute illness. • Safety during pregnancy has not been determined, so benefits must be weighed against potential risk.
Td, Tdap (Tetanus, diphtheria, pertussis) *Give IM*	• All adults who lack a history of a primary series consisting of at least 3 doses of tetanus- and diphtheria-containing vaccine. • A booster dose of tetanus- and diphtheria-containing toxoid may be needed for wound management as early as 5yrs after receiving a previous dose, so consult ACIP recommendations.* • Using tetanus toxoid (TT) instead of Td or Tdap is <u>not</u> recommended. • In pregnancy, when indicated, give Td or Tdap in 2nd or 3rd trimester. If not administered during pregnancy, give Tdap in immediate postpartum period. <u>For Tdap (tetanus- and diphtheria-toxoids with acellular pertussis vaccine) only:</u> • All adults younger than age 65yrs who have not received Tdap. • Healthcare workers who work in hospitals or ambulatory care settings and have direct patient contact and who have not received Tdap. • Adults in contact with infants younger than age 12m (e.g., parents, grandparents younger than age 65yrs, childcare providers, healthcare workers) who have not received a dose of Tdap.	• For persons who are unvaccinated or behind, complete the primary series with Td (spaced at 0, 1–2m, 6–12m intervals). One dose of Tdap may be used for any dose if ages 19–64yrs. • Give Td booster every 10yrs after the primary series has been completed. For adults ages 19–64yrs, a 1-time dose of Tdap is recommended to replace the next Td. • Intervals of 2yrs or less between Td and Tdap may be used if needed. **Note:** The 2 Tdap products are licensed for different age groups: Adacel (sanofi) for use in persons ages 11–64yrs and Boostrix (GSK) for use in persons ages 10–18yrs.	**Contraindications** • Previous anaphylactic reaction to this vaccine or to any of its components. • For Tdap only, history of encephalopathy within 7 days following DTP/DTaP. **Precautions** • Moderate or severe acute illness. • Guillain-Barré syndrome within 6wks of receiving a previous dose of tetanus toxoid-containing vaccine. • Unstable neurologic condition. **Note:** Use of Td or Tdap is not contraindicated in pregnancy. At the provider's discretion, either vaccine may be administered during the 2nd or 3rd trimester.
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 (i.e., India, Pakistan, Afghanistan, and certain countries in Africa). 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.

Summary of Recommendations for Adult Immunization (continued)

Vaccine name and route	For whom vaccination is recommended	Schedule for vaccine administration (any vaccine can be given with another)	Contraindications and precautions (mild illness is not a contraindication)
Varicella (Var) (Chickenpox) *Give SC*	All adults without evidence of immunity. Immunity is defined as any one of the following: • a history of two doses of Var • born in the U.S. before 1980 • history of varicella disease or herpes zoster based on healthcare provider diagnosis • laboratory evidence of immunity or laboratory confirmation of disease	• Two doses are needed. • Dose #2 is given 4–8wks after dose #1. • If Var and either MMR, LAIV, and/or yellow fever vaccine are not given on the same day, space them at least 28d 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. • 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.
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). • Microbiologists who are routinely exposed to isolates of *N. meningitidis.*	• One dose is needed. • If previous vaccine was MPSV4, revaccinate after 5yrs if risk continues. • Revaccination after MCV4 is not recommended. • MCV4 is preferred over MPSV4 for persons age 55yrs and younger, although MPSV4 is an acceptable alternative.	**Contraindication** Previous anaphylactic or neurologic reaction to this vaccine or to any of its components, including diphtheria toxoid (for MCV4). **Precautions** • Moderate or severe acute illness. • For MCV4 only, history of Guillain-Barré syndrome.
MMR (Measles, mumps, rubella) *Give SC*	• Persons born in 1957 or later (especially 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 (serology or vaccination) may be desirable for healthcare workers. • Women of childbearing age who do not have acceptable evidence of rubella immunity or vaccination.	• One or two doses are needed. • If dose #2 is recommended, give it no sooner than 4wks after dose #1. • If MMR and either Var, LAIV, and/or yellow fever vaccine are not given on the same day, space them at least 28d 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. • 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:** If PPD (tuberculosis skin test) and MMR are both needed but not given on same day, delay PPD for 4–6wks after MMR.
Human-papillomavirus (HPV) *Give IM*	All previously unvaccinated women through age 26yrs.	• Three doses are needed. • Dose #2 is given 4–8wks after dose #1, and dose #3 is given 6m after dose #1 (at least 12wks after dose #2).	**Contraindication** Previous anaphylactic reaction to this vaccine or to any of its components. **Precaution** Data on vaccination in pregnancy are limited; therefore, vaccination during pregnancy should be delayed until after completion of the pregnancy.
Zoster (shingles) (Zos) *Give SC*	A herpes zoster (shingles) vaccine was licensed in May 2006 for use in persons age 60yrs and older. ACIP recommendations for its use are pending. Refer to the package insert for details on its use.		

Suggested intervals between administration of **immune globulin preparations** and **measles-** or **varicella-containing vaccine***

*Does not include zoster vaccine (Zostavax)

Product / Indication	Dose, including mg immunoglobulin G (IgG)/kg body weight	Recommended interval before measles or varicella-containing vaccine administration
RSV monoclonal antibody (Synagis™)[1]	15 mg/kg intramuscularly (IM)	None
Tetanus IG (TIG)	250 units (10 mg IgG/kg) IM	3 months
Hepatitis A IG		
Contact prophylaxis	0.02 mL/kg (3.3.mg IgG/kg) IM	3 months
International travel	0.06 mL/kg (10 mg IgG/kg) IM	3 months
Hepatitis B IG (HBIG)	0.06 mL/kg (10 mg IgG/kg) IM	3 months
Rabies IG (RIG)	20 IU/kg (22 mg IgG/kg) IM	4 months
Measles prophylaxis IG		
Standard (i.e., nonimmunocompromised) contact	0.25 mL/kg (40 mg IgG/kg) IM	5 months
Immunocompromised contact	0.50 mL/kg (80 mg IgG/kg) IM	6 months
Blood tranfusion		
Red blood cells (RBCs), washed	10 mL/kg negligible IgG/kg intravenously (IV)	None
RBCs, adenine-saline added	10 mL/kg (10 mg IgG/kg) IV	3 months
Packed RBCs (Hct 65%)[2]	10 mL/kg (60 mg IgG/kg) IV	6 months
Whole blood (Hct 35%-50%)[2]	10 mL/kg (80-100 mg IgG/kg) IV	6 months
Plasma/platelet products	10 mL/kg (160 mg IgG/kg) IV	7 months
Cytomegalovirus intravenous immune globulin (IGIV)	150 mg/kg maximum	6 months
IGIV		
Replacement therapy for immune deficiencies[3]	300-400 mg/kg IV[3]	8 months
Immune thrombocytopenic purpura	400 mg/kg IV	8 months
Immune thrombocytopenic purpura	1000 mg/kg IV	10 months
Postexposure varicella prophylaxis[4]	400 mg/kg IV	8 months
Kawasaki disease	2 g/kg IV	11 months

This table is not intended for determining the correct indications and dosages for using antibody-containing products. Unvaccinated persons might not be fully protected against measles during the entire recommended interval, and additional doses of immune globulin or measles vaccine might be indicated after measles exposure. Concentrations of measles antibody in an immune globulin preparation can vary by manufacturer's lot. Rates of antibody clearance after receipt of an immune globulin preparation also might vary. Recommended intervals are extrapolated from an estimated half-life of 30 days for passively acquired antibody and an observed interference with the immune response to measles vaccine for 5 months after a dose of 80 mg IgG/kg.

1 Contains antibody only to respiratory syncytial virus.

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

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

4 The investigational product VariZIG, similar to licensed VZIG, is a purified human immune globulin preparation made from plasma containing high levels of anti-varicella antibodies (immunoglobulin class G [IgG]). When indicated, health-care providers should make every effort to obtain and administer VariZIG. In situations in which administration of VariZIG does not appear possible within 96 hours of exposure, administration of immune globulin intravenous (IGIV) should be considered as an alternative. IGIV also should be administered within 96 hours of exposure. Although licensed IGIV preparations are known to contain anti-varicella antibody titers, the titer of any specific lot of IGIV that might be available is uncertain because IGIV is not routinely tested for antivaricella antibodies. The recommended IGIV dose for postexposure prophylaxis of varicella is 400 mg/kg, administered once. For a pregnant woman who cannot receive VariZIG within 96 hours of exposure, clinicians can choose either to administer IGIV or closely monitor the woman for signs and symptoms of varicella and institute treatment with acyclovir if illness occurs. (CDC. A new product for postexposure prophylaxis available under an investigational new drug application expanded access protocol. *MMWR* 2006;55:209-10.)

Healthcare 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, pertussis	All adults need a Td booster dose every 10 years, following the completion of the primary 3-dose series. All HCWs younger than 65 years with direct patient contact should receive a 1-time dose of Tdap. Give IM.
Meningococcal	Give 1 dose to microbiologists who are routinely exposed to isolates of *N. meningitidis.*

Hepatitis A, typhoid, and polio vaccines are not routinely recommended for 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 hepatitis B virus (HBV) infection; revaccinate with a 3-dose series. Retest anti-HBs 1–2 months after dose #3.
  - If anti-HBs is positive, the patient is immune. No further testing or vaccination is recommended.
  - If anti-HBs is negative following 6 doses of vaccine, the patient is a non-responder.

For non-responders: 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.[1] 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 treated as if susceptible.[1]

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, mumps, and rubella.

- 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 and mumps vaccines separated by 28 days or more, and at least one dose of live rubella vaccine).
- Although birth before 1957 generally is considered acceptable evidence of measles, mumps, and rubella immunity, healthcare facilities should consider recommending a dose of MMR vaccine to unvaccinated HCWs born before 1957 who are in either of the following categories: (a) do not have a history of physician-diagnosed measles and mumps disease or laboratory evidence of measles and mumps immunity and (b) do not have laboratory evidence of rubella immunity.

Varicella

It is recommended that all HCWs be immune to varicella. Evidence of immunity in HCWs includes documentation of 2 doses of varicella vaccine given at least 28 days apart, history of varicella or herpes zoster based on physician diagnosis, laboratory evidence of immunity, or laboratory confirmation of disease.

Tetanus/Diphtheria/Pertussis (Td/Tdap)

All adults who have completed a 3-dose primary series of a tetanus/diphtheria-containing product (DTP, DTaP, DT, Td) should receive Td boosters every 10 years. As soon as feasible, HCWs younger than age 65 years with direct patient contact should be given a 1-time dose of Tdap.

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, MPSV is an acceptable alternative for persons ages 11–55 years. Use of MPSV is recommended for persons older than age 55; give SC.

References

1. See Table 3 in "Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HBV, HCV, and HIV and Recommendations for Postexposure Prophylaxis," *MMWR*, June 29, 2001, Vol. 50, RR-11.

For additional specific ACIP recommendations, refer to the official ACIP statements published in *MMWR*. To obtain copies, visit CDC's website at www.cdc.gov/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

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www.immunize.org/catg.d/p2017.pdf • Item #P2017 (1/07)

Immunization Action Coalition • 1573 Selby Ave. • St. Paul, MN 55104 • (651) 647-9009 • www.immunize.org • www.vaccineinformation.org

Vaccination of Persons with Primary and Secondary Immune Deficiencies

PRIMARY				
Category	**Specific Immunodeficiency**	**Contraindicated Vaccines[1]**	**Risk-Specific Recommended Vaccines[1]**	**Effectiveness & Comments**
B-lymphocyte (humoral)	Severe antibody deficiencies (e.g., X-linked agammaglobulinemia and common variable immunodeficiency)	OPV[2] Smallpox LAIV BCG Ty21a (live oral typhoid)	Pneumococcal Influenza (TIV) Consider measles and varicella vaccination.	The effectiveness of any vaccine will be uncertain if it depends only on the humoral response; IGIV interferes with the immune response to measles vaccine and possibly varicella vaccine.
	Less severe antibody deficiencies (e.g., selective IgA deficiency and IgG subclass deficiency	OPV[2] Other live vaccines appear to be safe.	Pneumococcal Influenza (TIV)	All vaccines probably effective. Immune response may be attenuated.
T-lymphocyte (cell-mediated and humoral)	Complete defects (e.g., severe combined immunodeficiency [SCID] disease, complete DiGeorge syndrome)	All live vaccines [3,4]	Pneumococcal Influenza (TIV)	Vaccines may be ineffective.
	Partial defects (e.g., most patients with DiGeorge syndrome, Wiskott-Aldrich syndrome, ataxia-telangiectasia)	All live vaccines [3,4]	Pneumococcal Meningococcal Hib (if not administered in infancy) Influenza (TIV)	Effectiveness of any vaccine depends on degree of immune suppression.
Complement	Deficiency of early components (C1-C4), late components (C5-C9), properdin, factor B.	None	Pneumococcal Meningococcal Influenza (TIV)	All routine vaccines probably effective.
Phagocytic function	Chronic granulomatous disease, leukocyte adhesion defects, and myeloperoxidase deficiency.	Live bacterial vaccines[3]	Pneumococcal[5] Influenza (TIV) (to decrease secondary bacterial infection).	All inactivated vaccines safe and probably effective. Live viral vaccines probably safe and effective.

[1] Other vaccines that are not specifically contraindicated may be used if otherwise indicated.
[2] OPV is no longer available for routine use in the United States.
[3] Live bacterial vaccines: BCG, and Ty21a *Salmonella typhi* vaccine.
[4] Live viral vaccines: MMR, OPV, LAIV, yellow fever, varicella (including MMRV and HZ vaccine), and vaccinia (smallpox). Smallpox vaccine is not recommended for children or the general public.
[5] Pneumococcal vaccine is not indicated for children with chronic granulomatous disease.

Vaccination of Persons with Primary and Secondary Immune Deficiencies

SECONDARY			
Specific Immunodeficiency	**Contraindicated Vaccines[1]**	**Recommended Vaccines[1]**	**Effectiveness & Comments**
HIV/AIDS	OPV[2] Smallpox BCG LAIV Withhold MMR and varicella in severely immunocompromised persons.	Influenza (TIV) Pneumococcal Consider Hib (if not administered in infancy) and Meningococcal vaccination.	MMR, varicella, and all inactivated vaccines, including inactivated influenza, might be effective.[3]
Malignant neoplasm, transplantation, immunosuppressive or radiation therapy	Live viral and bacterial, depending on immune status.[4,5]	Influenza (TIV) Pneumococcal	Effectiveness of any vaccine depends on degree of immune suppression.
Asplenia	None	Pneumococcal Meningococcal Hib (if not administered in infancy)	All routine vaccines probably effective.
Chronic renal disease	LAIV	Pneumococcal Influenza (TIV) Hepatitis B	All routine vaccines probably effective.

[1] Other vaccines that are not specifically contraindicated may be used if otherwise indicated.
[2] OPV is no longer available for routine use in the United States.
[3] HIV-infected children should receive IG after exposure to measles, and may receive varicella and measles vaccine if CD4+ lymphocyte count is ≥15%.
[4] Live viral vaccines: MMR, OPV, LAIV, yellow fever, varicella (including MMRV and HZ vaccine), and vaccinia (smallpox). Smallpox vaccine is not recommended for children or the general public.
[5] Live bacterial vaccines: BCG, and Ty21a *Salmonella typhi* vaccine.

AIDS: Acquired Immunodeficiency Syndrome
BCG: Bacilli Calmette-Guerin vaccine
Hib: *Haemophilus influenzae* type b vaccine
HIV: Human Immunodeficiency Virus
IGIV: Immune Globulin Intravenous
IG: Immunoglobulin
LAIV: Live, Attenuated Influenza Vaccine
MMR: Measles, Mumps, Rubella vaccine
OPV: Oral Poliovirus Vaccine (live)
TIV: Trivalent (inactivated) Influenza Vaccine

Modified from American Academy of Pediatrics. Passive Immunization. In: Pickering LK, Baker C, Long S, McMillen J, ed. *Red Book: 2006 Report of the Committee on Infectious Diseases*. 27th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2006: [71-72] and CDC. General Recommendations on Immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2006: 55 (No. RR-15).

Appendix A

APPENDIX B

Vaccines

U.S. Vaccines B1

Selected Discontinued U.S. Vaccines B4

Vaccine Excipient and Media Summary, by Excipient B6

Vaccine Excipient and Media Summary, by Vaccine B12

Thimerosal Content in Some U.S. Licensed Vaccines B15

Pediatric/VFC Vaccine Price List B16

Adult Vaccine Price List B18

Influenza Vaccine Price List B18

Foreign Language Terms B19

Appendix B

U.S. Vaccines

Vaccine	Name	Manufacturer	Type	Route	Comments
Anthrax	BioThrax	BioPort	Inactivated Bacterial	SC	
DTaP	Daptacel	sanofi	Inactivated Bacterial	IM	Tetanus & diphtheria toxoids and pertussis vaccine. Not licensed for 5th dose.
	Infanrix	GlaxoSmithKline	Inactivated Bacterial	IM	Tetanus & diphtheria toxoids and pertussis vaccine.
	Tripedia	sanofi	Inactivated Bacterial	IM	Tetanus & diphtheria toxoids and pertussis vaccine.
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). 3-dose schedule.
	PedvaxHIB	Merck	Inactivated Bacterial	IM	**PRP-OMP**. Polysaccharide conjugate (mening. protein carrier). 2-dose schedule.
	ActHIB	sanofi	Inactivated Bacterial	IM	**PRP-T**. Polysaccharide conjugate (tetanus toxoid carrier). 3-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. 3-dose series.
HepB/Hib	Comvax	Merck	Inactivated Bacterial & Viral	IM	Should not be used for HepB birth dose.
Human Papillomavirus (HPV)	Gardasil	Merck	Inactivated Viral (recombinant)	IM	Quadrivalent, Types 6, 11, 16 & 18. Licensed for females 9-26 years.
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.
	FluLaval	GlaxoSmithKline	Inactivated Viral	IM	Trivalent Types A & B. Minimum age = 18 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	Menomune	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	Merck	Inactivated bacterial	SC or IM	Polysaccharide. Contains 23 strains. Minimum age = 2 yrs.
	Prevnar	Wyeth	Inactivated bacterial	IM	Polysaccharide conjugate (diphtheria protein carrier). Contains 7 strains. Routine age range = 2-59 months.

Vaccine	Name	Manufacturer	Type	Route	Comments
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	
Rotavirus	RotaTeq	Merck	Live viral	Oral	Pentavalent. Age range 6-32 weeks. First dose between 6 & 12 weeks; complete 3-dose series by 32 weeks.
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	
Zoster (Shingles)	Zostavax	Merck	Live viral	SC	Licensed for age 60 and older.

December 2006

Selected *Discontinued* U.S. Vaccines

Trade Name	Antigen(s)	Years
Acel-Imune	DTaP	1991-2001
Attenuvax-Smallpox	Measles-Smallpox	1967
b-CAPSA-1	Hib (polysaccharide)	1985-89
Biavax	Rubella-Mumps (live)	
Cendevax	Rubella (live)	1969-79
Certiva	DTaP	1998-2000
Dip-Pert-Tet	DTP	
Diptussis	Diphtheria/Pertussis	1949-55
Ecolarix	Measles-Rubella (live)	
Flu Shield	Influenza	
Fluogen	Influenza	
Heptavax-B	Hepatitis B (plasma derived)	1981-90
HIB-Immune	Hib (polysaccharide)	1985-89
HIB-Vax	Hib (polysaccharide)	1985-89
Liovax	Smallpox	
Lirubel	Measles-Rubella (live)	1974-78
Lirugen	Measles (live)	1965-76
Lymerix	Lyme disease	1998-2002
M-Vac	Measles	1963-79
M-M-Vax	Measles-Mumps (live)	1973
Meningovax	Meningococcal	
Mevilin-L	Measles (live)	
MOPV	Polio (live, oral -monovalent, types I, II, & III)	
Mumpsvax	Mumps (live)	
OmniHIB	Hib (conjugate)	
Orimune	Polio (live, oral)	1961-2000

Trade Name	Antigen(s)	Years
Perdipigen	Diphtheria/Pertussis	1949-55
Pfizer-Vax Measles-K	Measles (inactivated)	1963-68
Pfizer-Vax Measles-L	Measles (live)	1965-70
Pnu-Imune	Pneumococcal (polysaccharide 14- or 23-valent)	1977-83
Poliovax	Polio (inactivated)	1988-91
ProHIBIT	Hib (conjugate)	1987-2000
Purivax	Polio (inactivated)	1956-65
Quadrigen	DTP-Polio	1959-68
Rabies Iradogen	Rabies	1908-57
RotaShield	Rotavirus	1998-99
Rubelogen	Rubella (live)	1969-72
Rubeovax	Measles (live)	1963-71
Serobacterin	Pertussis	1945-54
Solgen	DTP	1962-77
Tetra-Solgen	DTP-Polio	1959-68
Tetramune	DTP-Hib	
Tetravax	DTP-Polio	1959-65
Topagen	Pertussis (intranasal)	
Tri-Immunol	DTP	
Tridipigen	DTP	
Trinfagen No. 1	DT-Polio	Early 1960s
Trinivac	DTP	1952-64
Trivivac	DTP	
Wyvac	Rabies	1982-85

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 (*Act-HIB*)
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-isooctyl-phenyl 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

References: Canadian National Advisory Committee on Immunization. Statement on thimerosal. *Can Comm Dis Rep*. 2003;29(ACS-1):1-10.

CDC. Thimerosal in vaccines: a joint statement of the American Academy of Pediatrics and the Public Health Service. *MMWR*. 1999;48:563-565.

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Offit PA, Jew RK. Addressing parents's concerns: Do vaccines contain harmful preservatives, adjuvants, additives, or residuals. *Pediatrics*. 2003;112:1394-1401.

Reprinted courtesy of Grabenstein JD. *ImmunoFacts: Vaccines & Immunologic Drugs*. St. Louis, MO: Wolters Kluwer Health, Inc.; 2006.

Vaccine Excipient & Media Summary, Part 2

Excipients Included in U.S. Vaccines, by Vaccine

Includes vaccine ingredients (e.g., adjuvants and preservatives) as well as substances used during the manufacturing process, including vaccine-production media, that are removed from the final product and present only in trace quantities. In addition to the substances listed, most vaccines contain Sodium Chloride (table salt).

Vaccine	Contains
Anthrax (BioThrax)	Aluminum Hydroxide, Amino Acids, Benzethonium Chloride, Formaldehyde or Formalin, Inorganic Salts and Sugars, Vitamins
BCG (Tice)	Asparagine, Citric Acid, Lactose, Glycerin, Iron Ammonium Citrate, Magnesium Sulfate, Potassium Phosphate
DTaP (Daptacel)	Aluminum Phosphate, Ammonium Sulfate, Casamino Acid, Dimethyl-beta-cyclodextrin, Formaldehyde or Formalin, Glutaraldehyde, 2-Phenoxyethanol
DTaP (Infanrix)	Aluminum Hydroxide, Bovine Extract, Formaldehyde or Formalin, Glutaraldhyde, 2-Phenoxyethanol, Polysorbate 80
DTaP (Tripedia)	Aluminum Potassium Sulfate, Ammonium Sulfate, Bovine Extract, Formaldehyde or Formalin, Gelatin, Polysorbate 80, Sodium Phosphate, Thimerosal*
DTaP/Hib (TriHIBit)	Aluminum Potassium Sulfate, Ammonium Sulfate, Bovine Extract, Formaldehyde or Formalin, Gelatin, Polysorbate 80, Sucrose, Thimerosal*
DTaP/HepB/IPV (Pediarix)	Aluminum Hydroxide, Aluminum Phosphate, Bovine Protein, Lactalbumin Hydrolysate, Formaldehyde or Formalin, Glutaraldhyde, Monkey Kidney Tissue, Neomycin, 2-Phenoxyethanol, Polymyxin B, Polysorbate 80, Thimerosal*, Yeast Protein
DT (sanofi)	Aluminum Potassium Sulfate, Bovine Extract, Formaldehyde or Formalin, Thimerosal (multi-dose) or Thimerosal* (single-dose)
DT (Massachusetts)	Aluminum Hydroxide, Formaldehyde or Formalin
Hib (ACTHib)	Ammonium Sulfate, Formaldehyde or Formalin, Sucrose
Hib (PedvaxHib)	Aluminum Hydroxyphosphate Sulfate
Hib (HibTITER)	Amino Acids, Ammonium Sulfate, Mineral Salts, Yeast Protein
Hib/Hep B (Comvax)	Amino Acids, Aluminum Hydroxyphosphate Sulfate, Dextrose, Formaldehyde or Formalin, Mineral Salts, Sodium Borate, Soy Peptone, Yeast Protein
Hep A (Havrix)	Aluminum Hydroxide, Amino Acids, Formaldehyde or Formalin, MRC-5 Cellular Protein, Neomycin Sulfate, 2-Phenoxyethanol, Phosphate Buffers, Polysorbate
Hep A (Vaqta)	Aluminum Hydroxyphosphate Sulfate, Bovine Albumin or Serum, DNA, Formaldehyde or Formalin, MRC-5 Cellular Protein, Sodium Borate
Hep B (Engerix-B)	Aluminum Hydroxide, Phosphate Buffers, Thimerosal*, Yeast Protein
Hep B (Recombivax)	Aluminum Hydroxyphosphate Sulfate, Amino Acids, Dextrose, Formaldehyde or Formalin, Mineral Salts, Potassium Aluminum Sulfate, Soy Peptone, Yeast Protein

Vaccine	Contains
HepA/HepB (Twinrix)	Aluminum Hydroxide, Aluminum Phosphate, Amino Acids, Dextrose, Formaldehyde or Formalin, Inorganic Salts, MRC-5 Cellular Protein, Neomycin Sulfate, 2-Phenoxyethanol, Phosphate Buffers, Polysorbate 20, Thimerosal*, Vitamins, Yeast Protein
Human Papillomavirus (HPV) (Gardasil)	Amino Acids, Amorphous Aluminum Hydroxyphosphate Sulfate, Carbohydrates, L-histidine, Mineral Salts, Polysorbate 80, Sodium Borate, Vitamins
Influenza (Fluarix)	Egg Albumin (Ovalbumin), Egg Protein, Formaldehyde or Formalin, Gentamicin, Hydrocotrisone, Octoxynol-10, α-Tocopheryl Hydrogen Succinate, Polysorbate 80, Sodium Deoxycholate, Sodium Phosphate, Thimerosal*
Influenza (Flulaval)	Egg Albumin (Ovalbumin), Egg Protein, Formaldehyde or Formalin, Sodium Deoxycholate, Phosphate Buffers, Thimerosal
Influenza (Fluvirin)	Beta-Propiolactone , Egg Protein, Neomycin, Polymyxin B, Polyoxyethylene 9-10 Nonyl Phenol (Triton N-101, Octoxynol 9), Thimerosal (multidose containers), Thimerosal* (single-dose syringes)
Influenza (Fluzone)	Egg Protein, Formaldehyde or Formalin, Gelatin, Octoxinol-9 (Triton X-100), Thimerosal (multidose containers)
Influenza (FluMist)	Chick Kidney Cells, Egg Protein, Gentamicin Sulfate, Monosodium Glutamate, Sucrose Phosphate Glutamate Buffer
IPV (Ipol)	Calf Serum Protein, Formaldehyde or Formalin, Monkey Kidney Tissue, Neomycin, 2-Phenoxyethanol, Polymyxin B, Streptomycin,
Japanese Encephalitis (JE-Vax)	Formaldehyde or Formalin, Gelatin, Mouse Serum Protein, Polysorbate 80, Thimerosal
Measles (Attenuvax)	Amino Acid, Bovine Albumin or Serum, Chick Embryo Fibroblasts, Gelatin, Glutamate, Human Albumin, Neomycin, Phosphate, Sodium Phosphate, Sorbitol, Sucrose, Vitamins
Meningococcal (Menactra)	Formaldehyde or Formalin, Phosphate Buffers
Meningococcal (Menomune)	Lactose, Thimerosal (10-dose vials only)
Mumps (Mumpsvax)	Amino Acid, Bovine Albumin or Serum, Chick Embryo Fibroblasts, Human Serum Albumin, Gelatin, Glutamate, Neomycin, Phosphate Buffers, Sorbitol, Sucrose, Vitamins
MMR (MMR-II)	Amino Acid, Bovine Albumin or Serum, Chick Embryo Fibroblasts, Human Serum Albumin, Gelatin, Glutamate, Neomycin, Phosphate Buffers, Sorbitol, Sucrose, Vitamins
MMRV (ProQuad)	Bovine Albumin or Serum, Gelatin, Human Serum Albumin, Monosodium L-glutamate, MRC-5 Cellular Protein, Neomycin, Sodium Phosphate Dibasic, Sodium Bicarbonate, Sorbitol, Sucrose, Potassium Phosphate Monobasic, Potassium Chloride, Potassium Phosphate Dibasic
Pneumococcal (Pneumovax)	Bovine Protein, Phenol
Pneumococcal (Prevnar)	Aluminum Phosphate, Amino Acid, Soy Peptone, Yeast Extract
Rabies (Biorab)	Aluminum Phosphate, Phosphate Buffers, Rhesus Fetal Lung Tissue, Thimerosal

Vaccine	Contains
Rabies (Imovax)	Human Serum Albumin, Beta-Propiolactone, MRC-5 Cellular Protein, Neomycin, Phenol Red (Phenolsulfonphthalein), Vitamins
Rabies (RabAvert)	Amphotericin B, Beta-Propiolactone , Bovine Albumin or Serum, Chicken Protein, Chlortetracycline, Egg Albumin (Ovalbumin), Ethylenediamine-Tetraacetic Acid Sodium (EDTA), Neomycin, Potassium Glutamate
Rotavirus (RotaTeq)	Cell Culture Media, Fetal Bovine Serum, Sodium Citrate, Sodium Phosphate Monobasic Monohydrate, Sodium Hydroxide Sucrose, Polysorbate 80
Rubella (Meruvax II)	Bovine Albumin or Serum, Gelatin, Human Serum Albumin, Neomycin, Phosphate Buffers, Sodium Phosphate, Sorbitol
Td (Decavac)	Aluminum Potassium Sulfate, Bovine Extract, Formaldehyde or Formalin, 2-Phenoxyethanol, Peptone, Thimerosal*
Td (Massachusetts)	Aluminum Hydroxide, Aluminum Phosphate, Formaldehyde or Formalin, Thimerosal (some multidose containers)
Tdap (Adacel)	Aluminum Phosphate, Formaldehyde or Formalin, Glutaraldehyde, 2-Phenoxyethanol
Tdap (Boostrix)	Aluminum Hydroxide, Bovine Extract, Formaldehyde or Formalin, Glutaraldehyde, Polysorbate 80
Typhoid (inactivated – Typhim Vi)	Disodium Phosphate, Monosodium Phosphate, Phenol, Polydimethylsilozone, Hexadecyltrimethylammonium Bromide
Typhoid (oral – Ty21a)	Amino Acids, Ascorbic Acid, Bovine Protein, Casein, Dextrose, Galactose, Gelatin, Lactose, Magnesium Stearate, Sucrose, Yeast Extract
Vaccinia (DryVax)	Bovine Albumin or Serum, Brilliant Green (historic), Chlortetracycline Hydrochloride, Dihydrostreptomycin Sulfate, Glycerin, Neomycin, Phenol, Polymyxin B
Varicella (Varivax)	Bovine Albumin or Serum, Ethylenediamine-Tetraacetic Acid Sodium (EDTA), Gelatin, Monosodium L-Glutamate, MRC-5 DNA and Cellular Protein, Neomycin, Potassium Chloride, Potassium Phosphate Monobasic, Sodium Phosphate Monobasic, Sucrose
Yellow Fever (YF-Vax)	Egg Protein, Gelatin, Sorbitol
Zoster (Zostavax)	Bovine Calf Serum, Hydrolyzed Porcine Gelatin, Monosodium L-glutamate, MRC-5 DNA and Cellular Protein, Neomycin, Potassium Phosphate Monobasic, Potassium Chloride, Sodium Phosphate Dibasic, Sucrose

January 2007

*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 and individual products' package inserts.

All reasonable efforts have been made to ensure the accuracy of this information, but manufacturers may change product contents before that information is reflected here.

Thimerosal Content in Some US Licensed Vaccines
updated October 16, 2006

Vaccine	Brand Name (click on the brand name for package insert)		Manufacturer	Thimerosal Concentration	Mercury mcg/0.5 ml
Anthrax	BioThrax		BioPort Corporation	**0**	**0**
DTaP	Tripedia		sanofi pasteur	*	*
	Infanrix		GlaxoSmithKline	**0**	**0**
	DAPTACEL		sanofi pasteur	**0**	**0**
DTaP-HepB-IPV	Pediarix		GlaxoSmithKline	*	*
DTaP-Hib	TriHIBit		sanofi pasteur	*	*
DTwP	All Products			.01%	25
DT	Diphtheria & Tetanus Toxoids Adsorbed USP	multi-dose	sanofi pasteur	.01%	25
		single dose		*	*
Td	DECAVAC		sanofi pasteur	*	*
	Tetanus and Diphtheria Toxoids Adsorbed		sanofi pasteur	*	*
Tdap	ADACEL		sanofi pasteur	0	0
	Boostrix		GlaxoSmithKline	**0**	**0**
Tetanus Toxoid	Tetanus Toxoid Adsorbed USP		sanofi pasteur	.01%	25
	Tetanus Toxoid Adsorbed Adult Use			.01%	25
	Booster			.01%	25
Hib	ActHIB		sanofi pasteur	**0**	**0**
	HibTITER		Wyeth-Ayerst	**0**	**0**
	PedvaxHIB liquid(2)		Merck	**0**	**0**
Hib/HepB	Comvax (3)		Merck	**0**	**0**
Hepatitis A	Havrix		GlaxoSmithKline	**0**	**0**
	Vaqta adult/pediatric		Merck	**0**	**0**
Hepatitis B	Engerix-B preservative free		GlaxoSmithKline	*	*
	Recombivax HB preservative free		Merck	**0**	**0**
Hep A-B	Twinrix		GlaxoSmithKline	*	*
HPV	Gardasil		Merck	**0**	**0**
Influenza 2006/7 Formula	Fluarix		GlaxoSmithKline	*	*
	FluLaval		GlaxoSmithKline	.01%	25
	FluMist		MedImmune	**0**	**0**
	Fluvirin		Chiron	.01%	25
	Fluzone	5 mL vial	sanofi pasteur	.01%	25
	Fluzone No Preservative	0.25 mL prefilled syringe		**0**	**0**
		0.5 mL prefilled syringe		**0**	**0**
		0.5 mL vial		**0**	**0**
IPV	IPOL		sanofi pasteur	**0**	**0**
Meningococcal	Menactra		sanofi pasteur	**0**	**0**
	MENOMUNE-A/C/Y/W-135	multi-dose	sanofi pasteur	.01%	25
		single dose		*	*
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**
	RabAvert		Chiron	**0**	**0**
	IMOVAX		sanofi pasteur	**0**	**0**
Rotavirus	RotaTeq		Merck	**0**	**0**
Typhoid Fever	Typhim Vi		sanofi pasteur	**0**	**0**
	Vivotif		Berna Biotch	**0**	**0**
Varicella Zoster	Varivax		Merck	**0**	**0**
	Zostavax		Merck	**0**	**0**
Yellow Fever	YF-VAX		sanofi pasteur	**0**	**0**

1. A concentration of 1:10,000 is equivalent to a 0.01% concentration. Thimerosal is approximately 50% Hg by weight. A 1:10,000 concentration contains 25 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. This vaccine may contain trace amounts (<0.3 mcg) of mercury left after post-production thimerosal removal; these amounts have no biological effect. JAMA 1999;282(18) and JAMA 2000;283(16).

For current version of this table, see http://www.vaccinesafety.edu/thi-table.htm

Pediatric/VFC Vaccine Price List

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	3/31/07	sanofi pasteur
DTaP/	Infanrix®	10 pack - 1 dose vials 5 pack - 1 dose T-L syringes. No Needle	$13.25 $13.25	$20.96 $21.44	3/31/07	GlaxoSmithKline
DTaP-Hep B-IPV*	Pediarix®	10 pack - 1 dose vials 5 pack - 1 dose T-L syringes. No Needle	$43.75 $43.75	$70.72 $70.72	3/31/07	GlaxoSmithKline
DTaP-Hib #	TriHIBit®	5 pack - 1 dose vials	$24.94	$44.72	3/31/07	sanofi pasteur
e-IPV•	IPOL®	10 dose vials 10-pack – 1 dose syringes, No Needle	$10.82 $10.82	$22.80 $26.34	3/31/07	sanofi pasteur
Hepatitis B-Hib^	COMVAX®	10 pack - 1 dose vials	$26.25	$43.56	3/31/07	Merck
Hepatitis A Pediatric•	VAQTA®	10 pack - 1 dose vials	$12.10	$30.37	3/31/07	Merck
Hepatitis A Pediatric•	Havrix®	10 pack - 1 dose vials 5 pack - 1 dose T-L syringes. No Needle	$12.25 $12.25	$28.74 $28.74	3/31/07	GlaxoSmithKline
Hepatitis A-Hepatitis B 18 only^	Twinrix®	10 pack - 1 dose vials 5 pack - 1 dose T-L syringes, No Needle	$38.57 $38.57	$78.16 $78.42	3/31/07	GlaxoSmithKline
Hepatitis B• Pediatric/Adolescent	ENGERIX B®	10 pack - 1 dose vials 5 pack - 1 dose T-L syringes, No Needle	$9.10 $9.10	$21.37 $21.37	3/31/07	GlaxoSmithKline
Hepatitis B• Pediatric/Adolescent	RECOMBIVAX HB®	10 pack - 1 dose vials	$9.00	$23.20	3/31/07	Merck
Hepatitis B 2 dose• Adolescent (11-15)	RECOMBIVAX HB®	10 pack - 1 dose vials	$24.25	$59.09	3/31/07	Merck
Hib•	PedvaxHIB®	10 pack - 1 dose vials	$10.62	$22.77	3/31/07	Merck
Hib•	ActHIB®	5 pack - 1 dose vials	$7.92	$22.53	3/31/07	sanofi pasteur
HPV - Quadrivalent Human Papillomavirus Types 6, 11, 16 and 18 Recombinant	Gardasil®	10 pack – 1 dose vials	$96.00	$119.75	3/31/07	Merck
Measles, Mumps, Rubella and Varicella (MMR-V) #	ProQuad®	10 pack – 1 dose vials	$74.85	$117.60	3/31/07	Merck
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	3/31/07	sanofi pasteur
Measles, Mumps and Rubella (MMR)/	MMRII®	10 pack - 1 dose vials	$17.28	$42.85	3/31/07	Merck
Pneumococcal 7-valent• (Pediatric)	Prevnar®	10 pack – 1 dose syringes, No Needle	$57.59	$73.70	3/31/07	Wyeth/Lederle

Rotavirus, Live, Oral, Pentavalent •	RotaTeq ®	10 pack - 1 dose 2mL tubes	$52.00	$63.25	3/31/07	Merck
Tetanus & Diphtheria Toxoids^	DECAVAC™	10 pack – 1 dose syringes No Needle 10 pack – 1 dose vials	$16.62 $16.62	$18.30 $18.30	3/31/07	sanofi pasteur
Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis/	BOOSTRIX	10 pack - 1 dose vials 5 pack - 1 dose TL syringes, No Needle	$30.75 $30.75	$36.25 $36.25	3/31/07	GlaxoSmithKline
Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis/	ADACEL	10 pack - 1 dose vials	$30.75	$35.75	3/31/07	sanofi pasteur
Varicella•	Varivax®	10 pack - 1 dose vials	$56.90	$71.11	3/31/07	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

These price lists are current as of October 31, 2006

Find current Vaccine Price Lists online at www.cdc.gov/nip/vfc/cdc_vac_price_list.htm

Adult Vaccine Price List

Vaccine	Brandname/ Tradename	Packaging	CDC Cost/ Dose	Private Sector Cost/ Dose	Contract End Date	Manufacturer
Hepatitis A Adult•	VAQTA®	1 dose vials 10 pack - 1 dose vials	$18.50 $18.50	$63.51 $59.99	6/30/07	Merck
Hepatitis A Adult•	Havrix®	10 pack - 1 dose vials 5 pack - 1 dose T-L syringes, No Needle	$19.33 $19.33	$54.98 $54.98	6/30/07	GlaxoSmithKline
Hepatitis A-Hepatitis B Adult^	Twinrix®	10 pack - 1 dose vials 5 pack - 1 dose T-L syringes, No Needle	$38.57 $38.57	$78.16 $78.42	6/30/07	GlaxoSmithKline
Hepatitis B-Adult•	RECOMBIVAX HB®	1 dose vials 10 pack - 1 dose vials	$20.23 $22.19	$59.70 $59.09	6/30/07	Merck
Hepatitis B-Adult•	ENGERIX-B®	10 pack - 1 dose vials 5 pack - 1 dose T-L syringes, No Needle	$25.35 $25.35	$50.35 $50.35	6/30/07	GlaxoSmithKline
Pneumococcal Polysaccharide (23 Valent)	Pneumovax®	10 pack - 5 dose vials	$14.65	$24.19	6/30/07	Merck
Tetanus & Diphtheria Toxoids¤^	Tetanus & Diphtheria Toxoids Adsorbed for Adults	15 dose vials	$11.36	$14.99	6/30/07	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

Vaccine	Brandname/ Tradename	Packaging	CDC Cost/ Dose	Private Sector Cost/ Dose	Contract End Date	Manufacturer
Influenza ¤ • (Age 6 months and older)	Fluzone®	10 dose vials	$10.153	$11.198	2/28/07	sanofi pasteur
Influenza • (Age 6-35 months)	Fluzone® Pediatric dose Preservative-free	10 pack - 1 dose syringes	$12.584	$13.613	2/28/07	sanofi pasteur
Influenza • (Age 36 months and older)	Fluzone® No-Preservative	10 pack - 1 dose syringes 10 pack – 1 dose vials	$13.55 $13.55	$14.663 $14.663	2/28/07	sanofi pasteur
Influenza ¤ • (Age 4 years and older)	Fluvirin®	10 dose vials	$9.71	$11.71	2/28/07	Chiron
Influenza • (Age 18 years and older)	Fluarix™	5 pack – 1 dose syringes	$12.00	$13.25	2/28/07	GlaxoSmithKline
Influenza • Live, Intranasal (Age 5-49 years)	FluMist®	10 pack – 1 dose sprayers	$17.70	$17.95 to $20.95	2/28/07	MedImmune

• Vaccine cost includes $0.75 per dose Federal Excise Tax
¤ Vaccines which contain Thimerosal as a preservative

Foreign Language Terms

Aids to translating foreign immunization records.

Table 1: **Disease, Vaccine, and Related Terms.** This table lists terms for vaccine-preventable diseases, vaccines, and other items that might be found on an immunization record, by language.

Table 2: **Trade Names.** This table lists the names of specific vaccines that are used, or have been used, internationally, along with the manufactuer and country or region, when known.

These tables have been adapted from lists developed by
the Minnesota Department of Health Immunization Program
(now maintained by the Immunization Action Coalition)
and the
Washington State Department of Health.

See also:
http://www.immunize.org/izpractices/p5120.pdf
http://www.immunize.org/izpractices/p5121.pdf
http://www.doh.wa.gov/cfh.immunize/documents/schmanul.pdf (Appendix E)

These lists are not comprehensive and, while we have checked and rechecked sources, we do not claim complete accuracy.

Foreign Language Terms

Table 1: Disease, Vaccine, and Related Terms

Albanian	
Difteria	Diphtheria
Fruthi	Measles
Pertusisi	Pertussis
Tetanozi	Tetanus
Arabic	
Alhasiba	Rubella
As'al	Pertussis
Athab	Mumps
Difteria	Diphtheria
El Safra	Hepatitis
Has 'ba	Measles
Shel'el	Polio
Bosnian	
Beseže	BCG
Detepe	DTP
Difterija	Diphtheria
Dječja paraliza	Polio
Gripa	Influenza
Male boginje	Rubella
Ospice	Measles
Rubeola	Rubella
Upala pluća	Pneumonia
Veliki boginje	Smallpox
Veliki kašalj	Pertussis
Zauške	Mumps
Žutica	Hepatitis
Croatian	
Beseže	BCG
Detepe	DTP
Difterija	Diphtheria
Dječja paraliza	Polio
Gripa	Influenza
Hri pavac	Pertussis
Kašalj hripavac	Pertussis
Upala pluća	Pneumonia
Veliki boginje	Smallpox
Vodene kozice	Varicella
Zapaljenje	Hepatitis
Zaušnjaci	Mumps
Žutica	Hepatitis
Czech	
Davivy Kasel	Pertussis
Difterie	Diphtheria
Hepatitida	Hepatitis
Parotitida	Mumps
Pertuse	Pertussis
Poliomyelitis	Polio
Spalnicky	Measles
Subinuira	Influenza
Zardenky	Rubella
Zaškrt	Diphtheria
Danish	
Bornelammelse	Polio
Difteritis	Diphtheria
DKTP	DTP + IPV
Faaresyge	Mumps
Kighoste	Pertussis
Leverbetaendelse	Hepatitis
Meslinger	Measles
Rode Hunde	Rubella
Stivkrampe	Tetanus

Dutch	
BMR	MMR
Bof	Mumps
Difterie	Diphtheria
Gelekoorts	Yellow fever
Gordelroos	Varicella
Griep	Influenza
Kinderverlamming	Polio
Kinkhoest	Pertussis
Longontsteking	Pneumonia
Mazelen	Measles
Pokken	Smallpox
Rode hond	Rubella
Stijfkramp	Tetanus
Tering	Tuberculosis
Ethopian (Oromiffaa)	
Cufaa	Tetanus
Difteeriyaa	Diphtheria
Gifira	Measles
Gifira farangli	Rubella
Laamsheesaa	Polio
Qakkee	Pertussis
Shimbiraa	Hepatitis
Finnish	
Hinkuyska	Pertussis
Jaykkakouristus	Tetanus
Kurkkumata	Diphtheria
Lapsihalvaus	Polio
Sikotauti	Mumps
Tuhkarokko	Measles
Vihurirokko	Rubella
French	
Coqueluche	Pertussis
Diphtérie	Diphtheria

DTC, DT Coq	DTP
Fievre jaune	Yellow Fever
Grippe	Influenza
l'Haemophilus b	Hib
Oreillons	Mumps
Poliomyélite	Polio
ROR	MMR
Rougeole	Measles
Rubéole	Rubella
Tétanos	Tetanus
Tuberculose	Tuberculosis
Variole	Smallpox
German	
Diphtherie	Diphtheria
FSME	Tick-borne encephalitis
Grippe	Influenza
Keuchhusten	Pertussis
Kinderlähmung	Polio
Masern	Measles
Pocken	Smallpox
Rötein	Rubella
Starrkramph	Tetanus
Tuberkulose	Tuberculosis
Wundstarrkrampf	Tetanus
Zei Genpeter	Mumps
Greek	
Διφθερίτιδα, Τέτανος και Κοκκύτης	DTP
Ο Αιμόφιλος της γρίππης τύπου Β	Hib
Μηνιγγοκοκκική Ασθένεα ομάδας C	Meningococcal (C)
Ιλαρά - Μαγουλάδες - Ερυθρά	MMR
Πολιομυελίτιδα	Polio
Τέτανος και Διφθερίτιδα	Td

Haitian Creole	
Difteri	Diphtheria
Epatit	Hepatitis
Flou	Influenza
Koklich	Pertussis
Lawoujòl, Laroujòl	Measles
Malmouton	Mumps
Polyo	Polio
Ribeyòl	Rubella
Saranpyon	Varicella
Tetanòs	Tetanus
Hmong	
Hawb pob	Pertussis
Kabmob siab hom B	Hepatitis B
Kub cer	Diphtheria
Qhua Maj	Rubella
Qhua Pias	Measles
Qog	Mumps
Tuag tes tuag taw	Polio
Ua npuag	Tetanus
Indonesian	
Batuk rejan	Pertussis
Beguk	Mumps
Biring Peluh	Rubella
Campak	Measles
Difteri	Diphtheria
Penyakit lumpuh	Polio
Radang hati	Hepatitis
Italian	
Antipolio inattivato	IPV
Difterite	Diphtheria
Emofilo b	Hib
Epatite	Hepatitis
Morbillo	Measles
MPR (morbillo, parotite, rosolia)	MMR
Parotite	Mumps
Pertosse	Pertussis
Poliomielite	Polio
Polmonite	Pneumonia
Rosolia	Rubella
Tetano	Tetanus
Tosse Asinina	Pertussis
Tubercolosi	Tuberculosis
Vaioloso	Smallpox
Japanese	
Fushin	Rubella
Hashika	Measles
Hashofu	Tetanus
Hyakaseki	Pertussis
Jifuteria	Diphtheria
Otafukukuaze	Mumps
Sh niamahi	Polio
Malay	
Batok rejan	Pertussis
Penyaakit bengok	Mumps
Sakit champak	Measles
Sakit rengkong	Diphtheria
Norwegian	
Difteri	Diphtheria
Kikhoste	Pertussis
Kopper	Smallpox
Kusma	Mumps
Leverbetennelse	Hepatitis
Meslinger	Measles
Poliomyelitt	Polio
Røde hunder	Rubella
Stivkrampe	Tetanus
Vannkopper	Varicella

Polish	
Błonicy, Błonica, Błonnica	Diphtheria
Dyfteria	Diphtheria
Gruzlica	Tuberculosis
Grypa	Influenza
Koklusz	Pertussis
Krztuscowi, Krztusiec	Pertussis
Odra	Measles
Ospa	Smallpox
Paraliz dzieciecy	Polio
Pojar German	Rubella
Pojarul, Pojarului	Measles
Przypominajace	Booster
Rozyczka	Rubella
Swinka	Mumps
Tezec, Tężcowi	Tetanus
Zapalenie pluc	Pneumonia
Zapalenie watroby	Hepatitis
Portugese	
Cachumba (papeira)	Mumps
Coqueluche	Pertussis
Difteria	Diphtheria
Gripe	Influenza
Hepatite	Hepatitis
Paralisia infantil	Polio
Parotidite epidémica	Mumps
Poliomielite	Polio
Rúbéola	Rubella
Sarampo	Measles
Tetânica, Tétano	Tetanus
Triplice	DTP
VAHB	Hepatitis B Vaccine
VAP	Polio Vaccine
VAS	Measles Vaccine
VASPR	MMR
VAT	Tetanus Vaccine
Romanian	
AR	Measles
Difteria (Difteriei)	Diphtheria
Di Te	DT
Di-Te-Per	DTP
Febra Galbena	Yellow Fever
Gripa	Influenza
Hepatita	Hepatitis
Holera	Cholera
Oreion, Oreionului	Mumps
Pneumoniei	Pneumonia
Poliomielitic	Polio
Rubeolei, Rubeola	Rubella
Rujeola, Rujeolei	Measles
Tetanos,Tetanosul, Tetanosului	Tetanus
Tuse convulsiva, Tusei convulsive	Pertussis
Varicelă, Varicelei	Varicella
Variola, Variolei	Smallpox
Russian	
Бцж	BCG
АКДС	DTP
Дифтерит, Дифтерия	Diphtheria
Гемоифлюс инфлюзнцы типа Б	Hib
Гепатит	Hepatitis
Грипп	Influenza
Корь	Measles
Свинка, Паротит	Mumps
Коклюш	Pertussis
Воспале лёгких Пневмония	Pneumonia

Полиомиелит	Polio
Краснуха	Rubella
Оспа	Smallpox
Столбняк, Столбняка	Tetanus
Туберкулез	Tuberculosis
Ветрянка	Varicella
Манту	Mantoux (TB test)
Вакцина	Vaccine
Вакцинация	Series
Ревакцинация	Booster
Samoan	
Mami	Mumps
Misela	Measles
Rupela	Rubella
Serbian	
Beseže	BCG
Detepe	DTP
Difterija	Diphtheria
Dječja paraliza	Polio
Gripa	Influenza
Hri pavac	Pertussis
Male boginje	Rubella
Pljuskavice, Kozice	Varicella
Upala pluća	Pneumonia
Veliki boginje	Smallpox
Veliki kašalj	Pertussis
Zapaljenje	Hepatitis
Zaušnjaci	Mumps
Žutica	Hepatitis
Slovak	
Chripka	Influenza
Cierny kasel	Pertussis
Diftéria	Diphtheria
DiTePe	DTP

Hepatitida	Hepatitis
Krzamak	Measles
Osypky	Measles
Parotitis	Mumps
Polyomyelitida	Polio
Priusnica	Mumps
Ruzienka	Rubella
Zápal' plüc	Pneumonia
Spanish	
Cólera	Cholera
Coqueluche	Pertussis
Difteria	Diphtheria
Doble Antigen	Td (Mexico)
Doble Viral	Measles-Rubella (Mexico)
Duple	DT (Cuba)
Gripe	Influenza
Hemófilo tipo b	Hib
Numonía	Pneumonia
Paperas, Parotiditis	Mumps
Poliomielitis	Polio
Pulmonía	Pneumonia
Rubéola	Rubella
Sarampión, Sarampión Comun	Measles
Sarampión Aleman	Rubella
SPR	MMR
Tetánica, Tétano	Tetanus
Pertussis	Tos Ferina
Varicela	Varicella
Viruela	Smallpox
Somali	
Bus-buska	Varicella
Cagaarshowga	Hepatitis
Cuno xanuun	Diphtheria

Dabayl	Polio
Duf	Polio
Furuq	Smallpox
Gowracato	Diphtheria
Gurra dhaabsis	Mumps
Hablobaas	Varicella
Haemophilus nooca b	Hib
Infilowense	Influenza
Jadeeco	Measles
Jadeeco been, Jadeeco jarmalka	Rubella
Joonis	Hepatitis
Kix	Pertussis
Qaamow-Qashiir	Mumps
Qaaxo-Tiibi	Tuberculosis
Qanja Barar	Mumps
Sambabaha	Pneumonia
Tallaakla Qaaxada	BCG
Taytano	Tetanus
Wareento	Pneumonia
Xiiqdheer	Pertussis
Swedish	
Difteri	Diphtheria
Duplex	DT
Gula Febern	Yellow fever
Kikhosta	Pertussis
Kolera	Cholera
Mässling, Masslingormerly	Measles
Păssjura	Mumps
Polio	Polio
Rŏda Hund	Rubella
Smittkoppor	Smallpox
Stelkramp	Tetanus
Trippel	DTP

Tagalog	
Beke	Mumps
Dipterya	Diphtheria
Pertusis	Pertussis
Polyo	Polio
Tetano	Tetanus
Tigdas	Measles
Turkish	
Boğmaca	Pertussis
Çocuk Felci	Polio
DBT	DPT
Difteri	Diphtheria
Grýp	Influenza
KKK	MMR
Kabakulak	Rubella
Kýzamýk	Measles
Kýmamýkçýk	Mumps
Pnömokok	Pneumococcal
Su Çýçeğý	Varicella
Tetanos	Tetanus
Ýnfluenza	Influenza
Ukranian	
Кір	Measles
Поліо	Polio
Стовóняк	Tetanus
Vietnamese	
Bach Hâu	Diphtheria
Bai liet	Polio
Ban Đo	Rubella
Dai	Rabies
Ho Gà	Pertussis
Quai Bi	Mumps
Sài Uon Ván	Tetanus
So'i	Measles

Sot Tê Liêt	Polio
Thuong hàn	Typhoid
Uon ván	Tetanus
Viêm gan siêu vi B (VGSV B)	Hepatitis B
VNNB	Japapese encephalitis

Foreign Language Terms

Table 2: Trade Names

Trade name	Antigen(s)	Manufacturer, Country
A.D.T.	Diphtheria, tetanus (adsorbed)	Commonwealth, Australia
A.K.D.S.	Diphtheria, tetanus, pertussis	UK
ACVax	Meningococcal (polysaccharide A & C)	GSK, UK
ACWYVax	Meningococcal (polysaccharide A, C, W, Y135)	GSK, UK
Acelluvax	Pertussis (acellular)	Chiron, Italy
ACTAcel	Diphtheria, tetanus, pertussis, Hib	Sanofi Pasteur, Argentina
Adifteper	Diphtheria, tetanus, pertussis	Ism, Italy
Adinvira A+B	Influenza (whole virus)	Imuna
Adiugrip	Influenza	Sanofi Pasteur
Admun	Influenza (whole virus)	Duncan
Admune GP	Influenza (whole virus)	Duncan
Agrippal	Influenza	Socopharm
Aimmugen	Hepatitis A (inactivated)	Chemo-Sero-Therapeutic Resh Inst, Japan
Aldiana	Diphtheria (absorbed)	Sevac, Czech Republic
Alditeana	Diphtheria, tetanus (absorbed)	Sevac, Czech Republic
Alditerpera	Diphtheria, tetanus (adsorbed), pertussis	Sevac, Czech Republic
Almevax	Rubella	Evans
Alorbat	Influenza (whole virus)	Asta Pharma
Alteana Sevac	Tetanus	Institute of Sera and Vaccines
Amaril	Yellow fever	Sanofi Pasteur, France
AmBirix	Hepatitis A, Hepatitis B	GSK, Europe
AMC	Hib (polysaccharide)	Cuba
Anadifterall	Diphtheria (adsorbed)	Chiron, Italy
Anatetall	Tetanus (adsorbed)	Chiron, Italy
Anatoxal Di Te	Diphtheria, tetanus	Berna Biotech, Europe
Anatoxal Di Te Per	Diphtheria, tetanus, pertussis	Berna Biotech, Europe
Arilvax	Yellow fever	MEDI, UK
AVAC-1, AVA	Anthrax	(for U.S. military use)
AVAXIM	Hepatitis A	Aventis Pasteur, France
B-Hepavac II	Hepatitis B	Merck, Singapore
Begrivac	Influenza (split virus)	Chiron, Germany
Betagen	Hepatitis B	Sanofi Pasteur

Trade name	Antigen(s)	Manufacturer, Country
Biaflu Zonale	Influenza (whole virus)	Farmabiagini, Itali
Biken-HB	Hepatitis B	Biken, Japan
Bilive	Hepatitis A/Hepatitis B (Recombinant)	Sinovac, China
Bimmugen	Hepatitis B (recombinant, adsorbed, yeast derived)	Chemo-Sero-Therapeutic Resh Inst, Japan
Biviraten Berna	Measles, mumps (live)	Berna Biotech, Switzerland
Buccopol Berna	Polio (oral)	Berna Biotech, Europe
BVAC	Botulinum antitoxin	(for U.S. military use)
B-Vaxin	Hepatitis B	Laboratorios Pablo Cassara, Argentina
C.D.T.	Diphtheria, tetanus (pediatric, adsorbed)	Commonwealth, Australia
CEF	Measles (Schwarz strain)	Chiron, Italy
Cacar	Smallpox	Indonesia
Campak Kerig	Measles	Pasteur Institute, Indonesia
Celluvax	Pertussis (acellular)	Chiron, Italy
Cinquerix	Diphtheria, tetanus, pertussis, Hib, Polio	GSK, Europe
Cocquelucheau	Pertussis (adsorbed)	Sanofi Pasteur, France
D-Immun	Diphtheria	Osterreichisches Institut, Austria
D.S.D.P.T.	Diphtheria, tetanus, pertussis (adsorbed)	Dong Shin Pharm, Korea
D.T. Bis Rudivax	Diphtheria, tetanus, rubella	Sanofi Pasteur, France
Di Anatoxal	Diphtheria	Berna Biotech, Europe
Di Te Per Pol Impfstoff	Diphtheria, tetanus, pertussis, polio	Berna Biotech, Switzerland
Di-Te-Pol SSI	Diphtheria, tetanus, polio	Statens Seruminstitut, Denmark
Dif-Tet-All	Diphtheria, tetanus	Chiron, Italy
Diftavax	Diphtheria, tetanus	Sanofi Pasteur
Ditanrix	Diphtheria, tetanus	GSK, Europe
DiTe Anatoxal	Diphtheria, tetanus (adsorbed)	Berna Biotech, Switzerland
Ditoxim	Diphtheria, tetanus (adsorbed)	Dong Shin Pharm, Korea
Double Anigen B.I.	Diphtheria, tetanus	Bengal Immunity Co, India
DT Adulte	Diphtheria, tetanus (adult)	Sanofi Pasteur, France
DT Bis	Diphtheria, tetanus (booster)	Sanofi Pasteur, France
DT Coq	Diphtheria, tetanus, pertussis	Sanofi Pasteur, France
DT Polio	Diphtheria, tetanus, polio	Sanofi Pasteur, France
DT TAB	Diphtheria, tetanus, *Salmonella typhi, Paratyphi A & B*	Sanofi Pasteur, France
DT Vax	Diphtheria, tetanus (pediatric)	Sanofi Pasteur, France
DT Wellcovax	Diphtheria, tetanus (pediatric)	Chiron, UK

Trade name	Antigen(s)	Manufacturer, Country
Dual Antigen SII	Diphtheria, tetanus (adsorbed)	Serum Institute of India (India)
Dultavax	Diphtheria, tetanus, polio	Aventis Pasteur, France
Dupla	Diphtheria, tetanus	Instituto Butantan, Brazil
Duplex	Diphtheria, tetanus	Sweden
Ecolarix	Measles, rubella (Schwarz & RA 27/3)	GSK, Europe
Elvarix	Influenza (split virus)	VEB Sachsesches Serumwerk Dresden
Encepur	Tick-borne encephalitis	Chiron, Europe
Enivac-HB	Hepatitis B (Recombinant DNA)	Centro de Ingenieria Genetica Y Biotecnologia, Cuba
Enterovaccino	Typhoid (IM)	Isi
Eolarix	Measles, rubella (Schwarz & RA 27/3)	GSK, Europe
Epaxal Berna	Hepatitis A - virosomal vaccine	Berna Biotech, Switzerland
Ervax	Rubella (live)	GSK, Mexico
Ervevax RA 27/3	Rubella (live)	GSK, Belgium
Esavalenti	Diphtheria, tetanus, pertussis, polio, Hib, hepatitis B	Italy
Euvax-B	Hepatitis B (recombinant DNA)	LG Chemical, South Korea
Fendrix	Hepatitis B (dialysis formulation)	GSK, Europe
Fluad Agrippal-S1	Influenza	Chiron, Italy
Flubron	Influenza (whole virus)	Pfizer
Flugen	Influenza	UK
Fluvax	Influenza	CSL, Australia
Fluvirine	Influenza	CellTech Pharma SA
FOH-M	Polio (Inactivated)	Russia
FrocuoOke	Polio (Inactivated)	Russia
FSME-IMMUNE	Tick-borne encephalitis	Baxter, Austria
FSPD	Measles	Russia
Funed-CEME	Diphtheria, tetanus, pertussis	Belo Horizonte, Brazil
Gen H-B-Vax	Hepatitis B	Merck-Behringwerke
GenHevac B Pasteur	Hepatitis B	Sanofi Pasteur
Gripax	Influenza (whole virus)	Hebrew University
Gripe	Influenza (whole virus)	Spain
Gripovax	Influenza (whole virus)	GSK
Gunevax	Rubella	Chiron, Italy
H-Adiftal	Diphtheria	Ism, Italy
H-Adiftetal	Diphtheria, tetanus (adult)	Ism, Italy

Trade name	Antigen(s)	Manufacturer, Country
H-Atetal	Tetanus	Ism, Italy
HarPaBreHnr B CtauOHAP	Rubella	Russia
HAVPur	Hepatitis A	Chiron, Germany
HB Vax Pro	Hepatitis B	SP
HBY	Hepatitis B (recombinant)	KGC, Japan
Heberbiovac HB	Hepatitis B	Heberbiotec, Cuba
Hepabest	Hepatitis A	Sanofi Pasteur, Mexico
Hepacare	Hepatitis B (recombinant)	Chiron, Europe
Hepaccine-B	Hepatitis B (plasma derived)	Chiel Jedang, South Korea
Hepagene	Hepatitis B	Chiron, Europe
Hepativax	Hepatitis B	LG Life Sciences, Korea
Hepavax-B	Hepatitis B (plasma derived)	Korea Green Cross, South Korea
Hepavax-Gene	Hepatitis B (recombinant DNA)	Korea Green Cross, South Korea
Hepcare	Hepatitis B	Chiron, Europe
Heprecomb	Hepatitis B (yeast derived)	Berna Biotech, Switzerland
Hevac B	Hepatitis B (plasma derived)	Sanofi Pasteur, France
Hexavac (Hexavax)	Diphtheria, tetanus, pertussis, polio, hepatitis B, Hib	Sanofi Pasteur, Europe
Hiberix	Hib conjugate	GSK
HIBest	*Haemophilus influenzae* type b	Sanoti Pasteur
Hinkuys karokoe	Pertussis (adsorbed)	Natl. Public Health Institute, Finland
HIS	Influenza	Serbian Institute, Yugoslavia
IBV	Polio (inactivated)	Statens Seruminstitut, Denmark
Immravax	Measles, mumps, rubella	Sanofi Pasteur, Europe
Immugrip	Influenza	Pierre Fabre Médicament
Immunil	Pneumococcal (polysaccharide)	Sidus
Imovax Parotiditis	Mumps	Sanofi Pasteur, Europe
Imovax Polio	Polio	Sanofi Pasteur, Europe
Imovax Sarampion	Measles	Sanofi Pasteur, Europe
Imovax D.T.	Diphtheria, tetanus (adult)	Sanofi Pasteur, Europe
Imovax Gripe	Influenza	Sanofi Pasteur, Europe
Imovax R.O.R.	Measles, rubella, mumps (live)	Sanofi Pasteur, Europe
Imovax Rubeola	Measles	Sanofi Pasteur, Europe
Imovax Mumps	Mumps	Sanofi Pasteur, Europe
Imovax Oreillons	Mumps	Sanofi Pasteur, Europe

Trade name	Antigen(s)	Manufacturer, Country
Imovax Rage	Rabies vaccine	Sanofi Pasteur, Europe
Imovax Tetano	Tetanus	Sanofi Pasteur, Europe
Infanrix Hexa	DTaP, polio, Hib, hepatitis B	GSK, France
Infanrix Penta	DTaP, hepatitis B, polio	GSK, Europe
Infanrix Quinta	DTaP, polio, Hib	GSK, Europe
Infanrix Tetra	DTaP, polio	GSK, Europe
Inflexal	Influenza	Swiss Serum and Vaccine Institute
Influmix	Influenza (whole virus)	Schiapparelli
Influpozzi Zonale	Influenza (whole virus)	Ivp
Influsplit SSW	Influenza (split virus)	VEB Sachsecsches Serumwerk Dresden
Influvac	Influenza	Solvay-Pharma
Influvirus	Influenza	Ism, Italy
Invirin	Influenza (whole virus)	GSK
Ipad TP	Tetanus, polio	Sanofi Pasteur, France
IPV-Virelon	Polio (inactivated)	Chiron, Europe
Isiflu Zonale	Influenza (whole virus)	Isi, Italy
Istivac	Influenza	Sanofi Pasteur, Europe
Kaksoisrokote Dubbelvaccin	Diphtheria, tetanus (pediatric)	Natl. Public Health Institute, Finland
Kikhoste-Vaksine	Pertussis	Statens Institutt for Folkehelse, Norway
Koplivac	Measles (Edmonston strain)	Philips-Duphar, Australia
Kotipa	Cholera, typhoid, paratyphoid	Perum Bio Farma, Indonesia
Krztuscowi	Pertussis	(Poland)
Ksztu	Pertussis	(Poland)
Lancy Vaxina	Smallpox	Swiss Serum and Vaccine Institute, Switzerland
Lavantuu tirokote	Typhoid	Central Pub Health La, Finland
Liomorbillo	Measles	
Liovaxs	Smallpox	Chiron, Italy
Lirugen	Measles	Sanofi Pasteur
LM - 3 RIT	Measles, mumps, rubella (live)	Dong Shin Pharm, Korea
LM - 2 RIT	Measles, mumps (live)	Dong Shin Pharm, Korea
Lteanas Imuna	Tetanus (adsorbed)	Imuna sp., Slovakia
Lyssavac N	Rabies	Berna Biotech, Europe
M-M-Rvax	Measles, mumps, rubella	Chiron, Europe
M-M-Vax	Measles, mumps	Merck, Europe

Trade name	Antigen(s)	Manufacturer, Country
Masern-Impfstoff SSW	Measles (live)	Chiron, Germany
Massling	Measles	Sweden
MDPH-PA	Anthrax	
Measavac	Measles (Edmonston strain)	Pfizer, UK
Mencevax A	Meningococcal (polysaccharide) (Group A)	SmithKline/RIT, Belgium
Mencevax ACWY	Meningococcal quadravalent	GSK
Mengivax A/C	Meningococcal (conjugate) (Groups A & C)	Sanofi Pasteur, Europe
Meningitec	Meningococcal (conjugate) (Group C)	Wyeth, UK, Australia
Meningtec	Meningococcal (conjugate) (Group C)	Wyeth, Canada
Meninvact	Meningococcus (conjugate) (Group C)	Sanofi Pasteur
Menjugate	Meningococcus (conjugate) (Group C)	Socopharm
Menpovax 4	Meningococcal (polysaccharide) (Groups A, C, Y & W135)	Chiron, Europe
Menpovax A+C	Meningococcal (Groups A & C)	Chiron, Italy
Mesavac	Measles (Edmonston strain)	Pfizer, UK
Mevilin-L	Measles (Schwarz strain)	Chiron, UK
MFV	Influenza (whole virus)	Servier, UK
MFV-Ject	Influenza (whole virus)	Sanofi Pasteur, Europe
Miniflu	Influenza	Schiapparelli, Italy
Mo-Ru Viraten	Measles, rubella	Berna Biotech, Canada
Moniarix	Pneumococcal (polysaccharide)	GSK, Europe
Monovax / Monovac	BCG	Sanofi Pasteur, France
Mopavac	Measles, mumps (live, attenuated)	Sevac, Czech Republic
Morbilvax	Measles (live, attenuated)	Chiron, Italy
Morubel	Measles, rubella (live, attenuated)	Chiron, Italy
Moruman Berna	Measles immunoglobulin	Berna, Switzerland
Morupar	Measles, mumps, rubella (live, attenuated)	Chiron, Italy
Movivac	Measles (live, attenuated)	Sevac, Czech Republic
Mumaten	Mumps (live)	Berna Biogech, Switzerland
Munevan	Influenza (whole virus)	Medeva
Mutagrip	Influenza	Sanofi Pasteur, Germany
Nasoflu	Influenza	GSK, Europe
Neis Vac-C	Meningococcal (conjugate) (Group C)	Baxter, Europe & Canada
Neotyf	Typhoid (oral)	Chiron, Italy
Nivgrip	Influenza (whole virus)	Nicolau Institute of Virology, Romania

Trade name	Antigen(s)	Manufacturer, Country
NorHOMHerHTA	Polio (Inactivated)	Russia
Nothav	Hepatitis A	Chiron, Italy
Okavax	Varicella	Sanofi Pasteur, Japan & Europe
Oral Virelon	OPV	Chiron, Germany
Pariorix	Mumps (live)	GSK, Mexico & Europe
Pavivac	Mumps (live)	Sevac, Czech Republic
Pediacel	DTaP, Hib, IPV	Europe
Penta	Diphtheria, tetanus, (acellular) pertussis, Hib, IPV	Sanofi Pasteur, Europe
PENT-HIBest	Diphtheria, tetanus, pertussis, polio, Hib	Sanofi Pasteur
Pentacel	Diphtheria, tetanus, pertussis, polio, Hib	Sanofi Pasteur, Canada
Pentacoq	Diphtheria, tetanus, pertussis, polio, Hib	Sanofi Pasteur
PentAct-HIB	Diphtheria, tetanus, pertussis, polio, Hib	Sanofi Pasteur, Europe
Pentavac	Diphtheria, tetanus, pertussis, polio, Hib	Sanofi Pasteur
Pentavalente	Diphtheria, tetanus, pertussis, hepatitis B, Hib	Mexico
Pentavalenti	Diphtheria, tetanus, pertussis, polio, Hib OR Diphtheria, tetanus, pertussis, polio, hepatitis B	Italy
Pentaxim	Diphtheria, tetanus, pertussis, polio, Hib	Aventis Pasteur, France
Pluserix	Measles, rubella	GSK, Mexico & Europe
Pneumopur	Pneumococcal (polysaccharide)	Chiron, Europe
POLIAcel	Diphtheria, tetanus, pertussis, polio, HIB	Sanofi Pasteur, Argentina
Poliomyelite	Polio (inactivated)	France
Polioral	Polio (oral)	Chiron, Germany
Polio Sabin	Polio (oral)	GSK, Europe
Poloral	Polio (oral)	Swiss Serum and Vaccine Institute
Prevenar	Pneumococcal (7-valent, conjugate)	Wyeth, France
Previgrip	Influenza	Chiron France
Primavax	Diphtheria, tetanus, hepatitis B	Sanofi Pasteur, Europe
Priorix	Measles, mumps, rubella (live)	GSK, Europe & Australia
Priorix-Tetra	Measles, mumps, rubella, varicella	GSK, Europe
Probivac-B	Hepatitis B	Probiomed, Mexico
Procomvax	Hib, hepatitis B	Merck, Sanofi Pasteur, Europe
Pulmovax	Pneumococcal (polysaccharide)	Merck
Quadracel	Diphtheria, tetanus, pertussis, polio	Sanofi Pasteur, Mexico
QUADRAcel/Hibest	Diphtheria, tetanus, pertussis, polio, Hib	Sanofi Pasteur, Argentina

Trade name	Antigen(s)	Manufacturer, Country
Quadravax	DTP + polio	GSK
Quatro-Virelon	Diphtheria, tetanus, pertussis, polio	Chiron, Europe
Quinivax-IN	Diphtheria, tetanus, pertussis, Hib, polio	Valda Laboratori, Europe
Quintuple	Diphtheria, tetanus, pertussis, Hib, Polio	GSK, Mexico
R-HB Vaccine	Hepatitis B (recombinant)	Mitsubishi Chem Corp, Japan
R-Vac	Rubella (live)	Serum Institute, India
Rabdomune	Rabies	Impdfstofwerke, Germany
Rabipur	Rabies	Chiron, Germany
Rabivac	Rabies	Chiron, Germany
Rasilvax	Rabies	Chiron, Italy
RDCV	Rabies	
Repevax	DTaP, IPV	Sanofi Pasteur
Revaxis	Td, IPV	Sanofi Pasteur, Europe
Rimevax	Measles (live)	GSK, Mexico & Europe
Rimparix	Measles, mumps (live)	GSK, Europe
RIT - LM-2	Measles, mumps (live)	Dong Shin Pharm, Korea
RIT - LM-3	Measles, mumps, rubella (live)	Dong Shin Pharm, Korea
Rorvax	Measles, mumps, rubella (live)	Sanofi Pasteur, Europe & Brazil
Rosovax	Rubella	Ism, Italy
Rotarix	Rotavirus (serotype G1, P1A[P8]) Attenuated, clinical trial	GSK
Rouvax	Measles (live, attenuated)	Sanofi Pasteur, Europe
Rubavax	Rubella (live)	Sanofi Pasteur, UK
Rubeaten	Rubella (live)	Berna Biotech, Europe
Rubellovac	Rubella	Chiron, Germany
Rubilin	Rubella (live)	Chiron, UK
Rudi-Rouvax	Measles, rubella (live)	Sanofi Pasteur, France
Rudivax	Rubella (live, attenuated)	Sanofi Pasteur, Europe
Sahia	Polio (live, oral)	Multiple manufacturers
Sampar	Plague	Sanofi Pasteur, Indonesia
Sandovac	Influenza	Sandoz, Austria
Serap	Diphtheria, tetanus, pertussis	Perum Bio Farma, Indonesia
Shanvac-B	Hepatitis B	Shantha, India
SMBV	Rabies	Sanofi Pasteur, Europe
Sii Triple Antigen	Diphtheria, tetanus, pertussis	Serum Institute, India

Trade name	Antigen(s)	Manufacturer, Country
Stamaril	Yellow fever (live, attenuated)	Sanofi Pasteur, Europe
Streptopur	Pneumococcal (polysaccharide)	Chiron, Europe
Subinvira	Influenza (split virus)	Imuna, Czech Republic
T. Polio	Tetanus toxoid, polio	SP (Canada)
T.A.B.	Typhoid, paratyphoid (A & B)	- Institute Pasteur, Tunisia - Egypt - Pharmaceutical Industries Corp, Burma
T-Immun	Tetanus (adsorbed)	Baxter, Germany
T-Vaccinol	Tetanus	Roehm Pharma, Germany
T-Wellcovax	Tetanus	Wellcopharm, Germany
Tanrix	Tetanus	GSK, Europe
Td-Pur	Tetanus, diphtheria	Chiron, Europe
Td-Virelon	Tetanus, diphtheria, polio	Chiron, Europe
Te Anatoxal	Tetanus	Berna Biotech, Switzerland
Telvaclptap	Tetanus	Yugoslavia
Tet-Aktiv	Tetanus	Tropon-Cutter, Germany
Tet-Tox	Tetanus	CSL Limited, Australia
Tetagrip	Tetanus, influenza	SP (France)
Tetamun SSW	Tetanus (fluid, nonadsorbed)	Veb Sachsisches Serumwerk, Germany
Tetamyn	Tetanus	Bioclon, Mexico
Tetanol	Tetanus (adsorbed)	Chiron, Sanofi Pasteur, Europe & Mexico
Tetanovac	Tetanus	Sanofi Pasteur, Mexico
Tetasorbat SSW	Tetanus (adsorbed)	Veb Sachsisches Serumwerk, Germany
Tetatox	Tetanus (adsorbed)	Berna Biotech, Italy
Tetavax	Tetanus (adsorbed)	Sanofi Pasteur, Europe
Tetracoq 05	Diphtheria, tetanus, pertussis, polio	Sanofi Pasteur, France
TetrAct-HIB	Diphtheria, tetanus, pertussis, Hib	Sanofi Pasteur, Europe
Tetravac Acellulaire	Diphtheria, tetanus, pertussis, polio	Sanofi Pasteur, Europe
Tetravalenti	Diphtheria, tetanus, pertussis, hepatitis B	Italy
Tetraxim	Tetanus, diphtheria, pertussis, polio	Sanofi Pasteur, Europe
Theracys	BCG	Aventis Pasteur, Canada
Ticovac	Tick-borne encephalitis	Baxter SA
Tifovax	Typhoid (Vi polysaccharide)	Sanofi Pasteur, Mexico
Titifica	Typhoid and para typhoid	Italy
TOPV	Trivalent oral polio vaccine	Multiple manufacturers and countries
Trenin DPT Behring	Diphtheria, tetanus, pertussis	Chiron Behring GmbH, Germany

Trade name	Antigen(s)	Manufacturer, Country
Tresivac	Measles, mumps, rubella	Serum Institute, India
Triacel	Diphtheria, tetanus, (acellular) pertussis	Sanofi Pasteur, Europe & Mexico
Triacelluvax	Diphtheria, tetanus, (acellular) pertussis	Chiron, Europe
Trimovax	Measles, mumps, rubella (live)	Sanofi Pasteur, Europe
Tripacel	Diphtheria, tetanus, (acellular) pertussis	Sanofi Pasteur, Europe
Triple antigen	Diphtheria, tetanus, pertussis	- Chowgule & Co., India - CSL Limited, Australia
Triple Sabin	Polio (live, oral)	Mexico
Triple	Diphtheria, tetanus, pertussis	Cuba, Mexico
Triple Viral	Measles, mumps, rubella	Mexico Immunology Institute, Croatia
Triplice (VT)	Diphtheria, tetanus, pertussis	Instituto Butantan, Brazil
Triplice Viral (VTV)	Measles, mumps, rubella	Instituto Butantan, Brazil
Triplovax	Measles, mumps, rubella	Sanofi Pasteur, Europe & Brazil
Tritanrix	DTwP	GSK
Tritanrix-HB	DTwP/hepatitis B	GSK, Mexico
Tritanrix-HB-Hib	DTwP/hepatitis B/Hib	GSK
Trivacuna Leti	Diphtheria, tetanus (adsorbed), pertussis	Laboratory Leti, Spain
Trivax	Diphtheria, tetanus (plain), pertussis	Chiron, UK
Trivax-AD	Diphtheria, tetanus (adsorbed), pertussis	Chiron, UK
Trivax-Hib	Diphtheria, tetanus, pertussis, Hib	GSK, Europe
Trivb	Diphtheria, tetanus, pertussis	Brazil
Triviraten	Measles, mumps, rubella (live, attenuated)	Berna Biotech, Switzerland
Trivivac	Measles, mumps, rubella (live, attenuated)	Sevac, Czech Republic
Trivivax	Measles, mumps, rubella	Sanofi Pasteur, Mexico
Tussitrupin Forte	Pertussis	Staatliches Institut, Germany
Tuvax	BCG	Japan BCG Laboratory, Japan
Tyne	BCG	Sweden
Typherix	Typhoid (Vi polysaccharide)	GSK, Europe & Australia
Typhopara-typhoidique	Typhoid and para typhoid	France
Typhoral-L	Typhoid (Ty21a oral)	Berna Biotech, Germany
Typh-Vax	Typhoid	CSL Limited, Australia
Va-Diftet	Diphtheria, tetanus	Finlay Vacunas y Sueros, Cuba
Va-Mengoc-BC	Meningococcal (Groups B & C)	Finlay Vacunas y Sueros, Cuba
Vac-DPT	Diphtheria, tetanus, pertussis	Bioclon, Mexico
Vaccin Difteric Adsorbit	Diphtheria toxoid (adsorbed)	Cantacuzino Institute, Romania

Trade name	Antigen(s)	Manufacturer, Country
Vaccin Rabique Pasteur	Rabies	Pasteur Vaccins
Vaccin Combinat Diftero-Tetanic	Diphtheria, tetanus (adsorbed)	Cantacuzino Institute, Romania
Vaccin tuberculeux attenue lyophilise	BCG	Sanofi Pasteur, France
Vaccinum Morbillorum Vivum	Measles (live)	Moscow Research Institute, Russia
Vacina Dupla	Diphtheria, tetanus	Instituto Butantan, Brazil
Vacina Triplice	Diphtheria, tetanus, pertussis	Instituto Butantan, Brazil
Vacina Triplice Viral	Measles, mumps, rubella	Brazil
Vacunol	Tetanus	Temis-Lostato, Brazil
Vakcin Sampar	Plague	Perum Bio Farma, Indonesia
Vaksin Cacar	Smallpox	Indonesia
Vaksin Serap	Diphtheria, tetanus, pertussis	Perum Bio Farma, Indonesia
Vaksin Campak Kerig	Measles (live, attenuated)	Perum Bio Farma, Indonesia
Vaksin Kotipa	Cholera, typhoid and paratyphoid A, B & C	Perum Bio Farma (Indonesia)
Vamoavax	Measles, mumps (live)	Institute of Immunology, Croatia
Varicella-RIT	Varicella	GSK, Europe
Varicellon	Varicella zoster immunoglobulin	Behringwerke Aktiengesellischaft, Germany
Varie	Smallpox (lyophilized)	Institute of Sera and Vaccine, Czech Republic
Varilrix	Varicella (live, Oka strain)	GSK, Europe & Mexico
Tax-Tet	Tetanus	Finlay Vacunas & Sueros, Cuba
Vaxem-Hib	Hib (polysaccharide)	Chiron, Europe
Vaxicoq	Pertussis (adsorbed)	Sanofi Pasteur, France
Vaxigrip	Influenza	Sanofi Pasteur, Europe & Australia
Vaxihaler-Flu	Influenza (inhaler)	Riker, UK
Vaxipar	Mumps (live)	Chiron, Italy
VCDT	Diphtheria, tetanus (pediatric)	Cantacuzino Institute, Romania
VDA Vaccin Difteric Adsorbit	Diphtheria	Cantacuzino Institut, Romania
Verorab	Rabies (purified vero cell)	Sanofi Pasteur, France
Vibriomune	Cholera	Duncan Flockhart, UK
Viralinte	Hepatitis B	Ivax Pharmaceuticals, Mexico
Virelon C	Polio (Inactivated)	Chiron, Germany
Virelon T 20	Polio (live, oral, trivalent)	Chiron, Germany
Virivac	Measles, mumps, rubella (live)	Merck, Finland

Trade name	Antigen(s)	Manufacturer, Country
Virovac Massling, Perotid, Rubella	Measles, mumps, rubella	Sweden
Vopix	OPV	PT Biofarma, Indonesia
VT (Vacina Triplice)	Diphtheria, tetanus, pertussis	Instituto Butantan, Brazil
VTV (Vacina Triplice Viral)	Measles, mumps, rubella	Brazil
VVR	Measles (live, attenuated)	Cantucuzino Institute, Romania
Welltrivax trivalente	Diphtheria, tetanus, pertussis	Spain
Zaantide	Diphtheria anti-toxin	Imunoloski Zavod, Croatia
Zaantite	Tetanus anti-toxin	Imunoloski Zavod, Croatia
Zaditeadvax	Diphtheria, tetanus	Imunoloski Zavod, Croatia
Zaditevax	Diphtheria, tetanus	Imunoloski Zavod, Croatia
Zamevax A+C	Meningococcal (polysaccharide, Groups A & C)	Imunoloski Zavod, Croatia
Zamovax	Measles (live)	Imunoloski Zavod, Croatia
Zamruvax	Measles, rubella (live)	Imunoloski Zavod, Croatia
Zapavax	Mumps	Imunoloski Zavod, Croatia
Zaruvax	Rubella (live)	Imunoloski Zavod, Croatia
Zatetravax	Diphtheria, tetanus, pertussis, parapertussis	Imunoloski Zavod, Croatia
Zatevax	Tetanus	Imunoloski Zavod, Croatia
Zatribavax	Diphtheria, tetanus, pertussis	Imunoloski Zavod, Croatia
Zatrivax	Measles, rubella, mumps (live)	Imunoloski Zavod, Croatia

APPENDIX C

Vaccine Storage & Handling

Vaccine Storage & Handling Recommendtions (November 2007). C-1

Manufacturer Quality Control Phone Numbers C-20

Checklist for Safe Vaccine Handling and Storage C-21

Vaccine Handling Tips C-22

Sample Refrigerator Warning Signs C-23

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Appendix C

VACCINE MANAGEMENT

Recommendations for Storage and Handling of Selected Biologicals

November 2007



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

CDC

CS113788

Appendix C

Contents

DT, Td 3

DTaP, DTaP/Hib, DTaP/HepB/IPV,Tdap 4

Hepatitis Vaccines: Hepatitis A, Hepatitis B, Hepatitis A/B, Hepatitis B/Hib 5

Hib 6

HPV 7

IPV 8

TIV 9

LAIV 10

MMR, MR, Measles Virus Vaccine, Mumps Virus Vaccine, Rubella Virus Vaccine 11

MMRV 12

MCV 13

MPSV 14

PCV 15

PPV 16

Rotavirus Vaccine 17

Varicella (Chickenpox) Vaccine 18

Zoster (Shingles) Vaccine 19

Manufacturer Quality Control Office Telephone Numbers 20

DT: Diphtheria, Tetanus Toxoids—Pediatric
Td: Tetanus, Diphtheria Toxoids—Adult

Shipping Requirements

Should be shipped in insulated container. Maintain temperature at 35° – 46°F (2° – 8°C). **Do not freeze or expose to freezing temperatures.**

Condition upon Arrival

Should not have been frozen or exposed to freezing temperatures. Refrigerate upon arrival.

If you have questions about the condition of the material at the time of delivery, you should 1) immediately place material in recommended storage; and 2) then follow your state health department immunization program policy and contact either the Manufacturer's Quality Control office or the immunization program for guidance.

Storage Requirements

Refrigerate immediately upon arrival. Store at 35° – 46°F (2° – 8°C). **Do not freeze or expose to freezing temperatures.**

Shelf Life

Check expiration date on vial or manufacturer-filled syringe.

Instructions for Use

Inspect visually for extraneous particulate matter and/or discoloration. If these conditions exist, the vaccine should not be used. Shake vial or manufacturer-filled syringe well before use. Discard vaccine if it cannot be resuspended with thorough agitation.

Shelf Life after Opening

Single-Dose Vials: The vaccine should be administered shortly after withdrawal from the vial.

Multidose Vials: Withdraw single dose of vaccine into separate sterile needle and syringe for each immunization. The vaccine should be administered shortly after withdrawal from the vial. Unused portions of multidose vials may be refrigerated at 35° – 46°F (2° – 8°C) and used until expired, if not contaminated or unless otherwise stated in the manufacturer's product information.

Manufacturer-Filled Syringes: The vaccine should be administered shortly after the needle is attached to the syringe.

Special Instructions

Rotate stock so that the earliest dated material is used first.

Note: All vaccine materials should be disposed of using medical waste disposal procedures. Contact the state health department for details.

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° – 46°F (2° – 8°C). **Do not freeze or expose to freezing temperatures.**

Condition upon Arrival

Should not have been frozen or exposed to freezing temperatures. Refrigerate upon arrival.

If you have questions about the condition of the material at the time of delivery, you should 1) immediately place material in recommended storage; and 2) then follow your state health department immunization program policy and contact either the Manufacturer's Quality Control office or the immunization program for guidance.

Storage Requirements

Refrigerate immediately upon arrival. Store at 35° – 46°F (2° – 8°C). **Do not freeze or expose to freezing temperatures.**

Shelf Life

Check expiration date on vial, or manufacturer-filled syringe.

Instructions for Reconstitution* or Use

Inspect visually for extraneous particulate matter and/or discoloration. If these conditions exist, the vaccine should not be used. Shake vial or manufacturer-filled syringe well before use. Discard vaccine if it cannot be resuspended with thorough agitation.

Shelf Life after Reconstitution* or Opening

Single-Dose Vials: The vaccine should be administered shortly after withdrawal from the vial.

Manufacturer-Filled Syringes: The vaccine should be administered shortly after the needle is attached to the syringe.

Special Instructions

Rotate stock so that the earliest dated material is used first.

Note: All vaccine materials should be disposed of using medical waste disposal procedures. Contact the state health department for details.

* DTaP/Hib (TriHIBit®) is ActHIB® (sanofi pasteur) reconstituted with Tripedia® (sanofi pasteur). Once reconstituted, this combination vaccine must be used within 30 minutes or discarded. The only DTaP vaccine that can be used to reconstitute ActHIB® is Tripedia®. No other brand of DTaP is approved for this use.

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° – 46°F (2° – 8°C). **Do not freeze or expose to freezing temperatures.**

Condition upon Arrival

Should not have been frozen or exposed to freezing temperatures. Refrigerate upon arrival.

If you have questions about the condition of the material at the time of delivery, you should 1) immediately place material in recommended storage; and 2) then follow your state health department immunization program policy and contact either the Manufacturer's Quality Control office or the immunization program for guidance.

Storage Requirements

Refrigerate immediately upon arrival. Store at 35° – 46°F (2° – 8°C). **Do not freeze or expose to freezing temperatures.**

Shelf Life

Check expiration date on vial or manufacturer-filled syringe.

Instructions for Use

Inspect visually for extraneous particulate matter and/or discoloration. If these conditions exist, the vaccine should not be used. Shake vial or manufacturer-filled syringe well before use. Discard vaccine if it cannot be resuspended with thorough agitation.

Shelf Life after Opening

Single-Dose Vials: The vaccine should be administered shortly after withdrawal from the vial.

Manufacturer-Filled Syringes: The vaccine should be administered shortly after the needle is attached to the syringe.

Special Instructions

Rotate stock so that the earliest dated material is used first.

Note: All vaccine materials should be disposed of using medical waste disposal procedures. Contact the state health department for details.

Hib: *Haemophilus influenzae* type b Conjugate Vaccine

Shipping Requirements

Should be shipped in insulated container. Maintain temperature at 35° – 46°F (2° – 8°C). **Do not freeze or expose to freezing temperatures.**

Condition upon Arrival

Should not have been frozen or exposed to freezing temperatures. Refrigerate upon arrival.

If you have questions about the condition of the material at the time of delivery, you should 1) immediately place material in recommended storage; and 2) then follow your state health department immunization program policy and contact either the Manufacturer's Quality Control office or the immunization program for guidance.

Storage Requirements

Vaccine: Refrigerate immediately upon arrival. Store at 35° – 46°F (2° – 8°C). **Do not freeze or expose to freezing temperatures.**

Diluent: May be refrigerated or stored at room temperature (68° – 77°F [20° – 25°C]). **Do not freeze or expose to freezing temperatures.**

Shelf Life

Check expiration date on vial.

Instructions for Reconstitution* or Use

Inspect visually for extraneous particulate matter and/or discoloration. If these conditions exist, the vaccine should not be used. Shake vial well before use. Discard vaccine if it cannot be resuspended with thorough agitation.

Shelf Life after Reconstitution* or Opening

Single-Dose Vials: The vaccine should be administered shortly after withdrawal from the vial.

Special Instructions

Rotate stock so that the earliest dated material is used first.

Note: All vaccine materials should be disposed of using medical waste disposal procedures. Contact the state health department for details.

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* ActHIB® (sanofi pasteur) reconstituted with 0.4% sodium chloride diluent should be used within 24 hours after reconstitution. If sanofi pasteur DTaP-Tripedia® is used to reconstitute ActHIB®, the TriHibit® vaccine must be used within 30 minutes of reconstitution. Only sanofi pasteur DTaP-Tripedia® or the diluent shipped with the product may be used to reconstitute the sanofi pasteur ActHIB® product. No other brand of DTaP is licensed for use in reconstitution of ActHIB®.

HPV: Human Papillomavirus Vaccine

Shipping Requirements

Should be shipped in insulated container. Maintain temperature at 35° – 46°F (2° – 8°C). **Do not freeze or expose to freezing temperatures.**

Condition upon Arrival

Should not have been frozen or exposed to freezing temperatures. Refrigerate upon arrival.

If you have questions about the condition of the material at the time of delivery, you should 1) immediately place material in recommended storage; and 2) then follow your state health department immunization program policy and contact either the Manufacturer's Quality Control office or the immunization program for guidance.

Storage Requirements

Refrigerate immediately upon arrival. Store at 35° – 46°F (2° – 8°C). **Do not freeze or expose to freezing temperatures.** Protect from light at all times.

Shelf Life

Check expiration date on vial or manufacturer-filled syringe.

Instructions for Use

Inspect visually for extraneous particulate matter and/or discoloration. If these conditions exist, the vaccine should not be used. Shake vial or manufacturer-filled syringe well before use. Discard vaccine if it cannot be resuspended with thorough agitation.

Shelf Life after Opening

Single-Dose Vials: The vaccine should be administered shortly after withdrawal from the vial.

Manufacturer-Filled Syringes: The vaccine should be administered shortly after the needle is attached to the syringe.

Special Instructions

Rotate stock so that the earliest dated material is used first.

Note: All vaccine materials should be disposed of using medical waste disposal procedures. Contact the state health department for details.

IPV: Inactivated Polio Vaccine

Shipping Requirements

Should be shipped in insulated container. Maintain temperature at 35° – 46°F (2° – 8°C). **Do not freeze or expose to freezing temperatures.**

Condition upon Arrival

Should not have been frozen or exposed to freezing temperatures. Refrigerate upon arrival.

If you have questions about the condition of the material at the time of delivery, you should 1) immediately place material in recommended storage; and 2) then follow your state health department immunization program policy and contact either the Manufacturer's Quality Control office or the immunization program for guidance.

Storage Requirements

Refrigerate immediately upon arrival. Store at 35° – 46°F (2° – 8°C). **Do not freeze or expose to freezing temperatures.**

Shelf Life

Check expiration date on vial or manufacturer-filled syringe.

Instructions for Use

Inspect visually for extraneous particulate matter and/or discoloration. If these conditions exist, the vaccine should not be used. Shake vial or manufacturer-filled syringe well before use. Discard vaccine if it cannot be resuspended with thorough agitation.

Shelf Life after Opening

Multidose Vials: Withdraw single dose of vaccine into separate sterile needle and syringe for each immunization. The vaccine should be administered shortly after withdrawal from the vial. Unused portions of multidose vials may be refrigerated at 35° – 46°F (2° – 8°C) and used until expired, if not contaminated or unless otherwise stated in the manufacturer's product information.

Manufacturer-Filled Syringes: The vaccine should be administered shortly after the needle is attached to the syringe.

Special Instructions

Rotate stock so that the earliest dated material is used first.

Note: All vaccine materials should be disposed of using medical waste disposal procedures. Contact the state health department for details.

TIV: Trivalent Inactivated Influenza Vaccine

Shipping Requirements

Should be shipped in insulated container. Maintain temperature at 35° – 46°F (2° – 8°C). **Do not freeze or expose to freezing temperatures.**

Condition upon Arrival

Should not have been frozen or exposed to freezing temperatures. Refrigerate upon arrival.

If you have questions about the condition of the material at the time of delivery, you should 1) immediately place material in recommended storage; and 2) then follow your state health department immunization program policy and contact either the Manufacturer's Quality Control office or the immunization program for guidance.

Storage Requirements

Refrigerate immediately upon arrival. Store at 35° – 46°F (2° – 8°C). **Do not freeze or expose to freezing temperatures.** Protect Fluarix® and FluLaval™ from light at all times by storing in original package.

Shelf Life

Formulated for use during current influenza season. Check expiration date on vial or manufacturer-filled syringe.

Instructions for Use

Inspect visually for extraneous particulate matter and/or discoloration. If these conditions exist, the vaccine should not be used. Shake vial or manufacturer-filled syringe well before use. Discard vaccine if it cannot be resuspended with thorough agitation.

Shelf Life after Opening

Single-Dose Vials: The vaccine should be administered shortly after withdrawal from the vial.

Multidose Vials: Withdraw single dose of vaccine into separate sterile needle and syringe for each immunization. The vaccine should be administered shortly after withdrawal from the vial. Unused portions of multidose vials may be refrigerated at 35° – 46°F (2° – 8°C) and used until expired, if not contaminated or unless otherwise stated in the manufacturer's product information.

Manufacturer-Filled Syringes: The vaccine should be administered shortly after the needle is attached to the syringe.

Special Instructions

Rotate stock so that the earliest dated material is used first.

Note: All vaccine materials should be disposed of using medical waste disposal procedures. Contact the state health department for details.

LAIV: Live Attenuated Influenza Vaccine

Shipping Requirements

Initially shipped to authorized distributors in the frozen state 5°F (-15°C). Shipped from the distributor to healthcare facilities in the refrigerated state at 35° – 46°F (2° – 8°C).

Condition upon Arrival

Refrigerate upon arrival.

If you have questions about the condition of the material at the time of delivery, you should 1) immediately place material in recommended storage; and 2) then follow your state health department immunization program policy and contact either the Manufacturer's Quality Control office or the immunization program for guidance.

Storage Requirements

Refrigerate immediately upon arrival. Store at 35° – 46°F (2° – 8°C). **Do not freeze or expose to freezing temperatures.** (If LAIV is inadvertently frozen, the vaccine should be moved immediately to the refrigerator and may be used until the expiration date printed on the package.)

Shelf Life

Formulated for use during current influenza season. Check expiration date on package.

Instructions for Use

LAIV is a colorless to pale yellow liquid and is clear to slightly cloudy; some particulates may be present but do not affect the use of the product. After removal of the sprayer from the refrigerator, remove the rubber tip protector. Follow manufacturer's instructions to deliver ½ dose into one nostril. Then remove the dose-divider clip and deliver the remainder of the dose into the other nostril.

Shelf Life after Opening

Single-Dose Sprayer: The vaccine should be administered shortly after removal from the refrigerator.

Special Instructions

Rotate stock so that the earliest dated material is used first.

Note: All vaccine materials should be disposed of using medical waste disposal procedures. Contact the state health department for details.

MMR: Measles/Mumps/Rubella Vaccine, MR: Measles/Rubella Vaccine, Measles Virus Vaccine, Mumps Virus Vaccine, Rubella Virus Vaccine

Shipping Requirements

Vaccine: Should be shipped in insulated container. Must be shipped with refrigerant. Maintain temperature at 50°F (10°C) or less. If shipped with dry ice, diluent must be shipped separately.

Diluent: May be shipped with vaccine, but do not place in container with dry ice.

Condition upon Arrival

Maintain at 50°F (10° C) or less. **Do not use warm vaccine.** Refrigerate upon arrival.

If you have questions about the condition of the material at the time of delivery, you should 1) immediately place material in recommended storage; and 2) then follow your state health department immunization program policy and contact either the Manufacturer's Quality Control office or the immunization program for guidance.

Storage Requirements

Vaccine: Refrigerate immediately upon arrival. Store at 35° – 46°F (2° – 8°C). Protect from light at all times, since such exposure may inactivate the vaccine viruses.

Diluent: May be refrigerated or stored at room temperature (68° – 77°F [20° – 25°C]). **Do not freeze or expose to freezing temperatures.**

Note: MMR vaccine may be stored in the refrigerator or freezer.

Shelf Life

Check expiration date on vial.

Instructions for Reconstitution and Use

Reconstitute just before use according to the manufacturer's instructions. Use only the diluent supplied to reconstitute the vaccine.

Shelf Life after Reconstitution, Thawing or Opening

Single-Dose Vials: After reconstitution, use immediately or store at 35° – 46°F (2° – 8°C) and protect from light. **Discard if not used within 8 hours of reconstitution.**

Multidose vials: Withdraw single dose of reconstituted vaccine into separate sterile needle and syringe for each immunization. The vaccine dose should be administered shortly after withdrawal from vial. Unused portions of multidose vials may be refrigerated at 35° – 46°F (2° – 8°C), but must be discarded if not used within 8 hours after reconstitution.

Special Instructions

Rotate stock so that the earliest dated material is used first.

Note: All vaccine materials should be disposed of using medical waste disposal procedures. Contact the state health department for details.

MMRV: Measles/Mumps/Rubella/Varicella Vaccine

Shipping Requirements

Vaccine: Should be shipped in insulated container. Must be shipped with dry ice only, at 5°F (-15°C) or colder. Should be delivered within 2 days.

Diluent: May be shipped with vaccine, but do not place in container with dry ice.

Condition upon Arrival

Should be frozen. Vaccine should remain at 5°F (-15°C) or colder until arrival at the healthcare facility. Dry ice should still be present in the shipping container when vaccine is delivered.

If you have questions about the condition of the material at the time of delivery, you should 1) immediately place material in recommended storage; and 2) then follow your state health department immunization program policy and contact either the Manufacturer's Quality Control office or the immunization program for guidance.

Storage Requirements

Vaccine: Freeze immediately upon arrival. Maintain vaccine in a continuously frozen state at 5°F (-15°C) or colder. **No freeze/thaw cycles are allowed with this vaccine.** Vaccine should only be stored in freezers or refrigerator/freezers with separate external doors and compartments. Acceptable storage may be achieved in standard household freezers purchased in the last 10 years, and standard household refrigerator/freezers with a separate, sealed freezer compartment. "Dormitory-style units" are not appropriate for the storage of MMRV vaccine. **Do not store lyophilized vaccine in the refrigerator. If lyophilized vaccine is inadvertently stored in the refrigerator, it should be used within 72 hours. Lyophilized vaccine stored at 35° – 46°F (2° – 8°C) which is not used within 72 hours should be discarded.**

Protect the vaccine from light at all times since such exposure may inactivate the vaccine viruses.

In order to maintain temperatures of 5°F (-15°C) or colder, it will be necessary in most refrigerator/freezer models to adjust 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° – 77°F [20° – 25°C]). **Do not freeze or expose to freezing temperatures.**

Shelf Life

Check expiration date on vial.

Instructions for Reconstitution and Use

Reconstitute just before use according to the manufacturer's instructions. Use only the diluent supplied to reconstitute the vaccine.

Shelf Life after Reconstitution, Thawing or Opening

Single-Dose Vials: Discard reconstituted vaccine if it is not used **within 30 minutes** of reconstitution. **Do not freeze reconstituted vaccine.**

Special Instructions

Rotate stock so that the earliest dated material is used first.

If this vaccine is stored at a temperature warmer than 5°F (-15°C), it will result in a loss of potency and a reduced shelf life. If a power outage or some other situation occurs that results in the vaccine storage temperature rising above the recommended temperature, the healthcare provider should contact Merck, the vaccine manufacturer, at 1-800-MERCK-90 for an evaluation of the product potency before using the vaccine.

Note: All vaccine materials should be disposed of using medical waste disposal procedures. Contact the state health department for details.

MCV: Meningococcal Conjugate Vaccine

Shipping Requirements

Should be shipped in insulated container. Maintain temperature at 35° – 46°F (2° – 8°C). **Do not freeze or expose to freezing temperatures.**

Condition upon Arrival

Should not have been frozen or exposed to freezing temperatures. Refrigerate upon arrival.

If you have questions about the condition of the material at the time of delivery, you should 1) immediately place material in recommended storage; and 2) then follow your state health department immunization program policy and contact either the Manufacturer's Quality Control office or the immunization program for guidance.

Storage Requirements

Refrigerate immediately upon arrival. Store at 35° – 46°F (2° – 8°C). **Do not freeze or expose to freezing temperatures.**

Shelf Life

Check expiration date on vial or manufacturer-filled syringe.

Instructions for Use

Inspect visually for extraneous particulate matter and/or discoloration. If these conditions exist, the vaccine should not be used. Shake vial or manufacturer-filled syringe well before use. Discard vaccine if it cannot be resuspended with thorough agitation.

Shelf Life after Opening

Single-Dose Vials: The vaccine should be administered shortly after withdrawal from the vial.

Manufacturer-Filled Syringes: The vaccine should be administered shortly after the needle is attached to the syringe.

Special Instructions

Rotate stock so that the earliest dated material is used first.

Note: All vaccine materials should be disposed of using medical waste disposal procedures. Contact the state health department for details.

MPSV: Meningococcal Polysaccharide Vaccine

Shipping Requirements

Should be shipped in insulated container. Maintain temperature at 35° – 46°F (2° – 8°C). **Do not freeze or expose to freezing temperatures.**

Condition upon Arrival

Should not have been frozen or exposed to freezing temperatures. Refrigerate upon arrival.

If you have questions about the condition of the material at the time of delivery, you should 1) immediately place material in recommended storage; and 2) then follow your state health department immunization program policy and contact either the Manufacturer's Quality Control office or the immunization program for guidance.

Storage Requirements

Vaccine: Refrigerate immediately upon arrival. Store at 35° – 46°F (2° – 8°C). **Do not freeze or expose to freezing temperatures.**

Diluent: May be refrigerated or stored at room temperature (68° – 77°F [20° – 25°C]). **Do not freeze or expose to freezing temperatures.**

Shelf Life

Check expiration date on vial.

Instructions for Reconstitution and Use

Reconstitute just before using according to the manufacturer's instructions. Use only the diluent supplied to reconstitute the vaccine.

Shelf Life after Reconstitution or Opening

Single-Dose Vials: Use **within 30 minutes** of reconstitution.

Multidose Vials: Unused portions of multidose vials may be refrigerated at 35° – 46°F (2° – 8°C) and used up to 35 days after reconstitution.

Special Instructions

Rotate stock so that the earliest dated material is used first.

Note: All vaccine materials should be disposed of using medical waste disposal procedures. Contact the state health department for details.

PCV: Pneumococcal Conjugate Vaccine

Shipping Requirements

Should be shipped in insulated container. Maintain temperature at 35° – 46°F (2° – 8°C). **Do not freeze or expose to freezing temperatures.**

Condition upon Arrival

Should not have been frozen or exposed to freezing temperatures. Refrigerate upon arrival.

If you have questions about the condition of the material at the time of delivery, you should 1) immediately place material in recommended storage; and 2) then follow your state health department immunization program policy and contact either the Manufacturer's Quality Control office or the immunization program for guidance.

Storage Requirements

Refrigerate immediately upon arrival. Store at 35° – 46°F (2° – 8°C). **Do not freeze or expose to freezing temperatures.**

Shelf Life

Check expiration date on vial or manufacturer-filled syringe.

Instructions for Use

Inspect visually for extraneous particulate matter and/or discoloration. If these conditions exist, the vaccine should not be used. Shake vial or manufacturer-filled syringe well before use. Discard vaccine if it cannot be resuspended with thorough agitation.

Shelf Life after Opening

Single-Dose Vials: The vaccine should be administered shortly after withdrawal from the vial.

Manufacturer-Filled Syringes: The vaccine should be administered shortly after the needle is attached to the syringe.

Special Instructions

Rotate stock so that the earliest dated material is used first.

Note: All vaccine materials should be disposed of using medical waste disposal procedures. Contact the state health department for details.

PPV: Pneumococcal Polysaccharide Vaccine

Shipping Requirements

Should be shipped in insulated container. Maintain temperature at 35° – 46°F (2° – 8°C). **Do not freeze or expose to freezing temperatures.**

Condition upon Arrival

Should not have been frozen or exposed to freezing temperatures. Refrigerate upon arrival.

If you have questions about the condition of the material at the time of delivery, you should 1) immediately place material in recommended storage; and 2) then follow your state health department immunization program policy and contact either the Manufacturer's Quality Control office or the immunization program for guidance.

Storage Requirements

Refrigerate immediately upon arrival. Store at 35° – 46°F (2° – 8°C). **Do not freeze or expose to freezing temperatures.**

Shelf Life

Check expiration date on vial.

Instructions for Use

Inspect visually for extraneous particulate matter and/or discoloration. If these conditions exist, the vaccine should not be used. Shake vial or manufacturer-filled syringe well before use. Discard vaccine if it cannot be resuspended with thorough agitation.

Shelf Life after Opening

Single-Dose Vials: The vaccine should be administered shortly after withdrawal from the vial.

Multidose Vials: Withdraw single dose of vaccine into separate sterile needle and syringe for each immunization. The vaccine should be administered shortly after withdrawal from the vial. Unused portions of multidose vials may be refrigerated at 35° – 46°F (2° – 8°C) and used until expired, if not contaminated or unless otherwise stated in the manufacturer's product information.

Special Instructions

Rotate stock so that the earliest dated material is used first.

Note: All vaccine materials should be disposed of using medical waste disposal procedures. Contact the state health department for details.

Rotavirus Vaccine

Shipping Requirements

Should be shipped in insulated container. Maintain temperature at 35° – 46°F (2° – 8°C). **Do not freeze or expose to freezing temperatures.**

Condition upon Arrival

Should not have been frozen or exposed to freezing temperatures. Refrigerate upon arrival.

If you have questions about the condition of the material at the time of delivery, you should 1) immediately place material in recommended storage; and 2) then follow your state health department immunization program policy and contact either the Manufacturer's Quality Control office or the immunization program for guidance.

Storage Requirements

Refrigerate immediately upon arrival. Store at 35° – 46°F (2° – 8°C). **Do not freeze or expose to freezing temperatures.** Protect from light at all times, since such exposure may inactivate the vaccine viruses.

Shelf Life

Check expiration date on package.

Instructions for Use

Each dose is supplied in a container consisting of a squeezable plastic, latex-free dosing tube with a twist-off cap, allowing for direct oral administration. The dosing tube is contained in a pouch. Remove the dosing tube from the pouch, screw the cap clockwise to puncture the tube, and screw the cap off counter-clockwise so that the liquid can be squeezed from the tube during oral administration of the vaccine.

Shelf Life after Opening

Pouched Single-Dose Tubes: The vaccine should be administered shortly after withdrawal from the refrigerator. The dosing tube should not be returned to the refrigerator once the screw cap has been removed.

Special Instructions

Rotate stock so that the earliest dated material is used first.

Note: All vaccine materials should be disposed of using medical waste disposal procedures. Contact the state health department for details.

Varicella (Chickenpox) Vaccine

Shipping Requirements

Vaccine: Should be shipped in insulated container. Must be shipped with dry ice only, at 5°F (-15°C) or colder. Should be delivered within 2 days.

Diluent: May be shipped with vaccine, but do not place in container with dry ice.

Condition upon Arrival

Should be frozen. Vaccine should remain at 5°F (-15°C) or colder until arrival at the healthcare facility. Dry ice should still be present in the shipping container when vaccine is delivered.

If you have questions about the condition of the material at the time of delivery, you should 1) immediately place material in recommended storage; and 2) then follow your state health department immunization program policy and contact either the Manufacturer's Quality Control office or the immunization program for guidance.

Storage Requirements

Vaccine: Freeze immediately upon arrival. Maintain vaccine in a continuously frozen state at 5°F (-15°C) or colder. **No freeze/thaw cycles are allowed with this vaccine.** Vaccine should only be stored in freezers or refrigerator/freezers with separate external doors and compartments. Acceptable storage may be achieved in standard household freezers purchased in the last 10 years, and standard household refrigerator/freezers with a separate, sealed freezer compartment. "Dormitory-style units" are not appropriate for the storage of varicella vaccine. **Do not store lyophilized vaccine in the refrigerator. If lyophilized vaccine is inadvertently stored in the refrigerator, it should be used within 72 hours. Lyophilized vaccine stored at 35° – 46°F (2° – 8°C) which is not used within 72 hours, should be discarded.**

Protect the vaccine from light at all times since such exposure may inactivate the vaccine virus.

In order to maintain temperatures of 5°F (-15°C) or colder, it will be necessary in most refrigerator/freezer models to turn the temperature dial down to the coldest setting. This may result in the refrigerator compartment temperature being lowered as well. Careful monitoring of the refrigerator temperature will be necessary to avoid freezing killed or inactivated vaccines.

Diluent: May be refrigerated or stored at room temperature (68° – 77°F [20° – 25°C]). **Do not freeze or expose to freezing temperatures.**

Shelf Life

Check expiration date on vial.

Instructions for Reconstitution and Use

Reconstitute just before use according to the manufacturer's instructions. Use only the diluent supplied to reconstitute the vaccine.

Shelf Life after Reconstitution, Thawing or Opening

Single-Dose Vials: Discard reconstituted vaccine if it is not used **within 30 minutes** of reconstitution. **Do not freeze reconstituted vaccine.**

Special Instructions

Rotate stock so that the earliest dated material is used first.

If this vaccine is stored at a temperature warmer than 5°F (-15°C), it will result in a loss of potency and a reduced shelf life. If a power outage or some other situation occurs that results in the vaccine storage temperature rising above the recommended temperature, the healthcare provider should contact Merck, the vaccine manufacturer, at 1-800-9-VARIVAX for an evaluation of the product potency before using the vaccine.

Note: All vaccine materials should be disposed of using medical waste disposal procedures. Contact the state health department for details.

Zoster (Shingles) Vaccine

Shipping Requirements

Vaccine: Should be shipped in insulated container. Must be shipped with dry ice only, at 5°F (-15°C) or colder. Should be delivered within 2 days.

Diluent: May be shipped with vaccine, but do not place in container with dry ice.

Condition upon Arrival

Should be frozen. Vaccine should remain at 5°F (-15°C) or colder until arrival at the healthcare facility. Dry ice should still be present in the shipping container when vaccine is delivered.

If you have questions about the condition of the material at the time of delivery, you should 1) immediately place material in recommended storage; and 2) then follow your state health department immunization program policy and contact either the Manufacturer's Quality Control office or the immunization program for guidance.

Storage Requirements

Vaccine: Freeze immediately upon arrival. Maintain vaccine in a continuously frozen state at 5°F (-15°C) or colder. **No freeze/thaw cycles are allowed with this vaccine.** Vaccine should only be stored in freezers or refrigerator/freezers with separate external doors and compartments. Acceptable storage may be achieved in standard household freezers purchased in the last 10 years, and standard household refrigerator/freezers with a separate, sealed freezer compartment. "Dormitory-style units" are not appropriate for the storage of zoster vaccine. **Do not store lyophilized vaccine in the refrigerator.** Protect the vaccine from light at all times since such exposure may inactivate the vaccine virus.

In order to maintain temperatures of 5°F (-15°C) or colder, it will be necessary in most refrigerator/freezer models to turn the temperature dial down to the coldest setting. This may result in the refrigerator compartment temperature being lowered as well. Careful monitoring of the refrigerator temperature will be necessary to avoid freezing killed or inactivated vaccines.

Diluent: May be refrigerated or stored at room temperature (68° – 77°F [20° – 25°C]). **Do not freeze or expose to freezing temperatures.**

Shelf Life

Check expiration date on vial.

Instructions for Reconstitution and Use

Reconstitute just before use according to the manufacturer's instructions. Use only the diluent supplied to reconstitute the vaccine.

Shelf Life after Reconstitution, Thawing or Opening

Single-Dose Vials: Discard reconstituted vaccine if it is not used **within 30 minutes** of reconstitution. **Do not freeze reconstituted vaccine.**

Special Instructions

Rotate stock so that the earliest dated material is used first.

If this vaccine is stored at a temperature warmer than 5°F (-15°C), it will result in a loss of potency and a reduced shelf life. If a power outage or some other situation occurs that results in the vaccine storage temperature rising above the recommended temperature, the healthcare provider should contact Merck, the vaccine manufacturer, at 1-800-MERCK-90 for an evaluation of the product potency before using the vaccine.

Note: All vaccine materials should be disposed of using medical waste disposal procedures. Contact the state health department for details.

Manufacturer Quality Control Office Telephone Numbers

Manufacturer/Distributor	Telephone Number	Products
sanofi pasteur www.sanofipasteur.us	800-822-2463	DTaP, DTaP-Hib, DT, Td, Tdap, TT, Hib, Influenza (TIV), IPV, MCV4, MPSV4
Talecris Biotherapeutics www.talecrisusa.com/	800-520-2807	HBIG, IGIM, RIG, TIG
Centers for Disease Control and Prevention Drug Service www.cdc.gov/ncidod/srp/drugs/drug-service.html	404-639-3670	Distributor for Diphtheria antitoxin
Novartis www.novartis-vaccines.com/products/index.shtml	800-244-7668	Influenza (TIV)
GlaxoSmithKline www.gsk.com/	866-475-8222 (customer support) 888-825-5249 (customer support)	DTaP, DTaP-HepB-IPV,Tdap, HepA, HepB, HepA-HepB, Influenza (TIV)
Massachusetts Biological Labs	617-474-3000 617-983-6400	Td, IGIM, TT
MedImmune, Inc. www.medimmune.com	877-358-6478	Influenza (LAIV)
Merck www.merckvaccines.com	800-637-2590	Hib, Hib-HepB, HepA, HepB, HPV, Measles, Mumps, Rubella, MMR, MMRV, PPV23, Rotavirus, Varicella, Zoster
Nabi Biopharmaceuticals www.nabi.com	800-635-1766	HBIG
Wyeth www.wyeth.com	800-999-9384	Hib, PCV7

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.
____	____	10.	We always keep a thermometer in the refrigerator.
____	____	11.	The temperature in the refrigerator is maintained at 35–46°F (2–8°C).
____	____	12.	We keep extra containers of water in the refrigerator to help maintain cold temperatures.
____	____	13.	We always keep a thermometer in the freezer.
____	____	14.	The temperature in the freezer is maintained at +5°F (-15°C) or colder.
____	____	15.	We keep ice packs and other ice-filled containers in the freezer to help maintain cold temperatures.
____	____	16.	We post a temperature log on the refrigerator door on which we record the refrigerator and freezer temperatures twice a day—first thing in the morning and at clinic closing time—and we know whom to call if the temperature goes out of range.
____	____	17.	We have a "Do Not Unplug" sign next to the refrigerator's electrical outlet.
____	____	18.	In the event of a refrigerator failure, we take the following steps: ____ We assure that the vaccines are placed in a location with adequate refrigeration. ____ We mark exposed vaccines and separate them from undamaged vaccines. ____ We note the refrigerator or freezer temperature and contact the vaccine manufacturer or state health department to determine how to handle the affected vaccines. ____ We follow the vaccine manufacturer's or health department's instructions as to whether the affected vaccines can be used, and, if so, we mark the vials with the revised expiration date provided by the manufacturer or health department.
____	____	19.	We have obtained a detailed written policy for general and emergency vaccine management from our local or state health department.
____	____	20.	If all above answers are "yes," we are patting ourselves on the back. If not, we have assigned someone to implement needed changes!

Technical content reviewed by the Centers for Disease Control and Prevention. Dec. 2006.

www.immunize.org/catg.d/p3035chk.pdf • Item #P3035 (12/06)

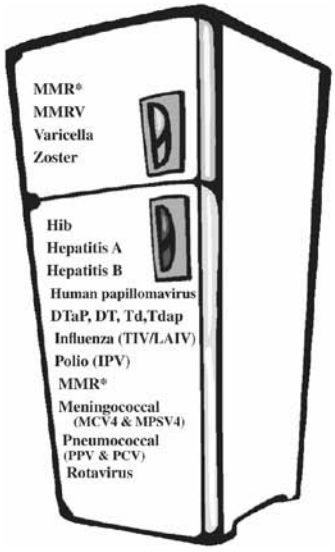
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Vaccine Handling Tips

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

Technical content reviewed by the Centers for Disease Control and Prevention, May 2007.

www.immunize.org/catg.d/p3048.pdf • Item #P3048 (5/07)

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WARNING

Do not unplug the refrigerator/
freezer or break circuit.
Expensive vaccine in storage.



In event of electrical problem, immediately contact:

WARNING

Do not unplug the refrigerator/
freezer or break circuit.
Expensive vaccine in storage.



In event of electrical problem, immediately contact:

WARNING

Do not unplug the refrigerator/
freezer or break circuit.
Expensive vaccine in storage.



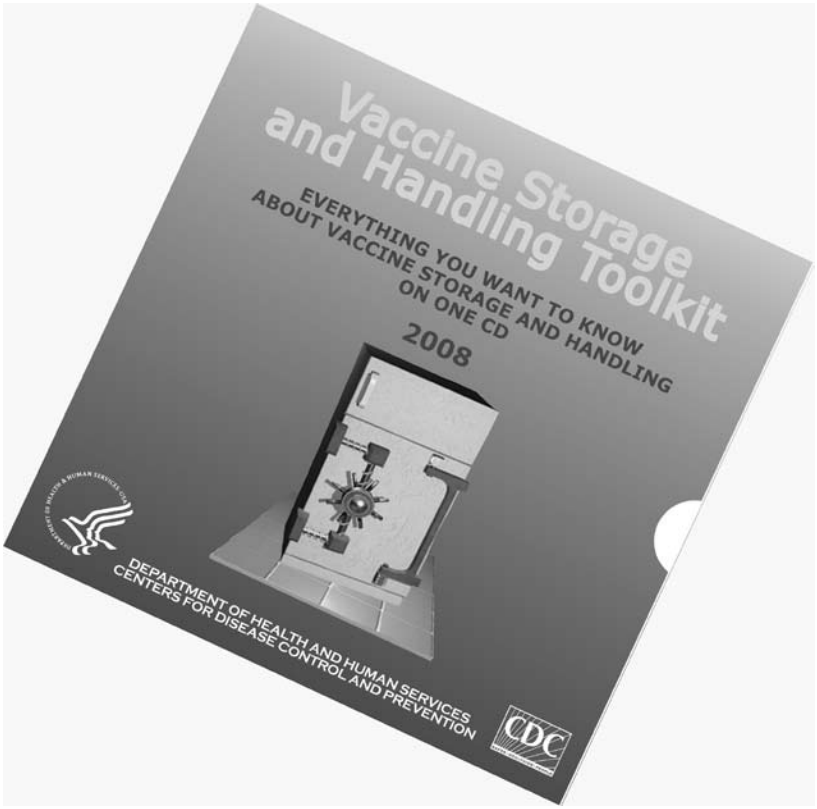
In event of electrical problem, immediately contact:

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/vaccines.pubs

APPENDIX D

Vaccine Administration

"Vaccine Administration" Guidelines D-1

Skills Checklist for Immunization D-14

Immunization Site Maps. D-16

Medical Management of Vaccine Reactions (Children & Teens) D-18

Medical Management of Vaccine Reactions (Adults) D-20

"Comforting Restraint" for Immunizations D-22

Appendix D

Vaccine Administration

Appropriate vaccine administration is critical to vaccine effectiveness. The recommended site, route and dosage for each vaccine are based on clinical trials, practical experience and theoretical considerations. The following information provides general guidelines for administration of vaccines for those who administer vaccines, as well as those in training, education and supervisory positions. This information should be used in conjunction with professional standards for medication administration, vaccine manufacturers' product guidelines, CDC's Advisory Committee on Immunization Practices (ACIP) General Recommendations on Immunization, the American Academy of Pediatrics' (AAP) Report of the Committee on Infectious Diseases *Red Book*, and state/agency-related policies and procedures. An education plan that includes competency-based training on vaccine administration should be considered for all persons who administer vaccines to children or adults (refer to "Skills Checklist for Immunization" - page D14).

Preparation

PATIENT PREPARATION - Patients should be prepared for vaccination with consideration for their age and stage of development. Parents/guardians and patients should be encouraged to take an active role before, during and after the administration of vaccines (see "Be There for Your Child During Shots" poster at http://cdlhn.com/default.htm, search for IMM674S).

- **Screening** - All patients should be screened for contraindications and precautions for each scheduled vaccine. Many state immunization programs and other organizations have developed and make available standardized screening tools. Basic screening questions can be found in Chapter 2. Sample screening forms for children and adults are available from the Immunization Action Coalition (www.immunize.org).

- **Vaccine Safety & Risk Communication** - Parents/guardians and patients are exposed through the media to information about vaccines, some of which is inaccurate or misleading. Healthcare providers should be prepared to discuss the benefits and risks of vaccines using Vaccine Information Statements (VIS) and other reliable resources. Establishing an open dialogue provides a safe, trust-building environment in which individuals can freely evaluate information, discuss vaccine concerns and make informed decisions regarding immunization (see Chapter 4 and Appendices E and F).

- **Atraumatic Care** - Vaccine safety issues and the need for multiple injections have increased the concerns and anxiety associated with immunizations. Healthcare providers need to display confidence and establish an environment that promotes a sense of security and trust for the patient and family, utilizing a variety of techniques to minimize the stress and discomfort associated with receiving injections. This is particularly important when administering vaccines to children.

  ► **Positioning & Comforting Restraint** - The healthcare provider must accommodate for the patient's comfort, safety, age, activity level, and the site of administration when

considering patient positioning and restraint. For a child, the parent/guardian should be encouraged to hold the child during administration. If the parent is uncomfortable, another person may assist or the patient may be positioned safely on an examination table (refer to "Comforting Restraint for Immunizations" - page D22).

► **Pain Control** - Pain is a subjective phenomenon influenced by multiple factors, including an individual's age, anxiety level, previous healthcare experiences, and culture. Consideration for these factors is important as the provider develops a planned approach to management of injection pain (see “Be There for Your Child During Shots” poster).

- *Topical Anesthetics* or a vapocoolant spray may be applied to decrease pain at the injection site. These products should be used only for the ages recommended and as directed by the product manufacturer.

- *Analgesic Agents* — A non-aspirin containing pain reliever may be considered to decrease discomfort and fever following vaccination. These products should be used only in age-appropriate doses.

- *Diversionary Techniques* - Age-appropriate non pharmacologic techniques may provide distraction from pain associated with injections. Diversion can be accomplished through a variety of techniques, some of which are outlined on the “Be There for Your Child During Shots” poster.

- *Dual Administrators* - Some providers favor the technique of two individuals simultaneously administering vaccines at separate sites. The premise is that this procedure may decrease anxiety from anticipation of the next injection(s). The effectiveness of this procedure in decreasing pain or stress associated with vaccine injections has not been evaluated.

INFECTION CONTROL - Healthcare providers should follow Standard Precautions to minimize the risks of spreading disease during vaccine administration.

- **Handwashing** - The single, most effective disease prevention activity is good handwashing. Hands should be washed thoroughly with soap and water or cleansed with an alcohol-based waterless antiseptic between patients, before vaccine preparation or any time hands become soiled, e.g. diapering, cleaning excreta.

- **Gloving** - Gloves are not required to be worn when administering vaccines unless the person administering the vaccine is likely to come into contact with potentially infectious body fluids or has open lesions on the hands. It is important to remember that gloves cannot prevent needlestick injuries.

- **Needlestick Injuries** should be reported immediately to the site supervisor, with appropriate care and follow-up given as directed by state/local guidelines. Safety needles or needle-free injection devices should be used if available to reduce the risk of injury.

- **Equipment Disposal** - Used needles should not be detached from syringes, recapped or cut before disposal. All used syringe/needle devices should be placed in puncture proof containers to prevent accidental needlesticks and reuse. Empty or expired vaccine vials are considered medical waste and should be disposed of according to state regulations.

VACCINE PREPARATION - Proper vaccine handling and preparation is critical in maintaining the integrity of the vaccine during transfer from the manufacturer's vial to the syringe and ultimately to the patient.

- **Equipment Selection**

  ►**Syringe Selection** - A separate needle and syringe should be used for each injection. A parenteral vaccine may be delivered in either a 1-mL or 3-mL syringe as long as the prescribed dosage is delivered. Syringe devices with sharps engineered sharps injury protection are 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 evaluation and selection of these products. Staff should receive training with these device before using them in the clinical area.

  ►**Needle Selection** - Vaccine must reach the desired tissue site for optimal immune response. Therefore, needle selection should be based upon the prescribed route, size of the individual, volume and viscosity of the vaccine, and injection technique. (See Subcutaneous & Intramuscular Injections, below.) Typically, vaccines are not highly viscous, and therefore a fine gauge needle (22–25 gauge) can be used.

  ►**Needle-Free Injection** - A new generation of needle-free vaccine delivery devices has been developed in an effort to decrease the risks of needlestick injuries to healthcare workers and to prevent improper reuse of syringes and needles. For more information on needle-free injection technology, see the CDC website: www.cdc.gov/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 unless otherwise stated on the package labeling. Expired vaccine should never be used.

- **Reconstitution** - Some vaccines are prepared in a lyophilized form that requires reconstitution, which should be done according to manufacturer guidelines. Diluent solutions vary; use only the specific diluent supplied for the vaccine. Once reconstituted, the vaccine must be either administered within the time guidelines provided by the manufacturer or discarded. Changing the needle after reconstitution of the vaccine is not necessary unless the needle has become contaminated or bent. Continue with standard medication preparation guidelines.

- **Prefilling Syringes** - CDC strongly discourages filling syringes in advance, because of the increased risk of administration errors. Once the vaccine is in the syringe it is difficult to identify the type or brand of vaccine. Other problems associated with this practice are vaccine wastage, and possible bacterial growth in vaccines that do not contain a preservative. Furthermore, medication administration guidelines state that the individual who administers a medication should be the one to draw up and prepare it. An alternative to prefilling syringes is to use filled syringes supplied by the vaccine manufacturer. Syringes other than those filled by the manufacturer are designed for immediate administration, not for vaccine storage.

  In certain circumstances, such as a large influenza clinic, more than one syringe can be filled. One person should prefill only a few syringes at a time, and the same person should administer them. Any syringes left at the end of the clinic day should be discarded.

  Under no circumstances should MMR, varicella, or zoster vaccines ever be reconstituted and drawn prior to the immediate need for them. These live virus vaccines are unstable and begin to deteriorate as soon as they are reconstituted with diluent.

- **Labeling** - Once a vaccine is drawn into a syringe, the content should be indicated on the syringe. There are a variety of methods for identifying or labeling syringes (e.g. keep syringes with the appropriate vaccine vials, place the syringes in a labeled partitioned tray, or use color coded labels or preprinted labels).

Administration

Route - Administering a vaccine by the recommended route is imperative. Deviation from the recommended route of administration might reduce vaccine efficacy or increase the risk of local reactions.

Administering Vaccines: Dose, Route, Site, and Needle Size

Vaccines	Dose	Route
Diphtheria, Tetanus, Pertussis (DTaP, DT, Tdap, Td)	0.5 mL	IM
***Haemophilus influenzae* type b (Hib)**	0.5 mL	IM
Hepatitis A (HepA)	≤18 yrs: 0.5 mL ≥19 yrs: 1.0 mL	IM
Hepatitis B (HepB) **Persons 11–15 yrs may be given Recombivax HB® (Merck) 1.0 mL adult formulation on a 2-dose schedule.*	≤19 yrs: 0.5 mL* ≥20 yrs: 1.0 mL	IM
Human papillomavirus (HPV)	0.5 mL	IM
Influenza, live attenuated (LAIV)	0.5 mL	Intranasal spray
Influenza, trivalent inactivated (TIV)	6-35 mos: 0.25 mL ≥3 yrs: 0.5 mL	IM
Measles, mumps, rubella (MMR)	0.5 mL	SC
Meningococcal, conjugated (MCV4)	0.5 mL	IM
Meningococcal, polysaccharide (MPSV4)	0.5 mL	SC
Pneumococcal conjugate (PCV)	0.5 mL	IM
Pneumococcal polysaccharide (PPV)	0.5 mL	IM or SC
Polio, inactivated (IPV)	0.5 mL	IM or SC
Rotavirus (Rv)	2.0 mL	Oral
Varicella (Var)	0.5 mL	SC
Zoster (Zos)	0.65 mL	SC
Combination Vaccines		
DTaP+HepB+IPV (Pediarix™) **DTaP+Hib (Trihibit™)** **Hib+HepB (Comvax™)**	0.5 mL	IM
MMR+Var (ProQuad®)	≤12 yrs: 0.5 mL	SC
HepA+HepB (Twinrix®)	≥18 yrs: 1.0 mL	IM

Injection Site and Needle Size

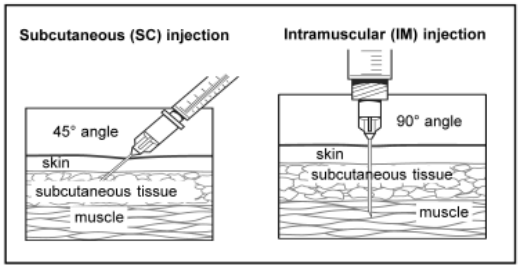
Subcutaneous (SC) injection
Use a 23–25 gauge needle. Choose the injection site that is appropriate to the person's age and body mass.

Age	Needle Length	Injection Site
Infants (1–12 mos)	⅝"	Fatty tissue over anterolateral thigh muscle
Children (≥12 mos), adolescents, & adults	⅝"	Fatty tissue over anterolateral thigh muscle or fatty tissue over triceps

Intramuscular (IM) injection
Use a 22–25 gauge needle. Choose the injection site and needle length appropriate to the person's age and body mass.

Age	Needle Length	Injection Site
Newborn (1st 28 days)	⅝"*	Anterolateral thigh muscle
Infant (1–12 mos)	1"	Anterolateral thigh muscle
Toddler (1–2 yrs)	1"–1¼" ⅝"*–1"	Anterolateral thigh muscle or deltoid muscle of arm
Children 3–18 yrs	⅝"*–1" 1"–1¼"	Deltoid muscle of arm or anterolateral thigh muscle
≥19 yrs (Sex/Weight)		
Male/Female less than 130 lbs	⅝"*–1"	Deltoid muscle of arm
Female (130–200 lbs) Male (130–260 lbs)	1"–1½"	Deltoid muscle of arm
Female (200+ lbs) Male (260+ lbs)	1½"	Deltoid muscle of arm

**If skin is stretched tight and subcutaneous tissue is not bunched.*

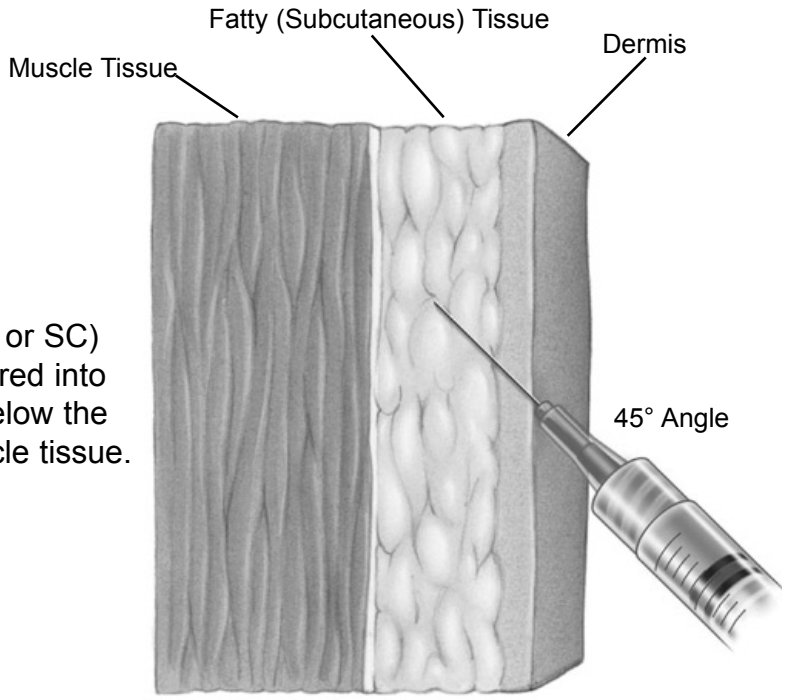


Please note: Always refer to the package insert included with each biologic for complete vaccine administration information. CDC's Advisory Committee on Immunization Practices (ACIP) recommendations for the particular vaccine should be reviewed as well.

Technical content reviewed by the Centers for Disease Control and Prevention, Nov. 2006.

www.immunize.org/catg.d/p3085.pdf • Item #P3085 (1/07)

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Lynne Larson, www.biovisuals.com

- **Subcutaneous** (Sub-Q or SC) injections are administered into the fatty tissue found below the dermis and above muscle tissue.

- **Site** - Subcutaneous tissue can be found all over the body. The usual sites for vaccine administration are the thigh (for infants <12 months of age) and the upper outer triceps of the arm (for persons ≥12 months of age). If necessary, the upper outer triceps area can be used to administer subcutaneous injections to infants.




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- **Needle Gauge & Length** - 5/8-inch, 23- to 25-gauge needle

- **Technique**

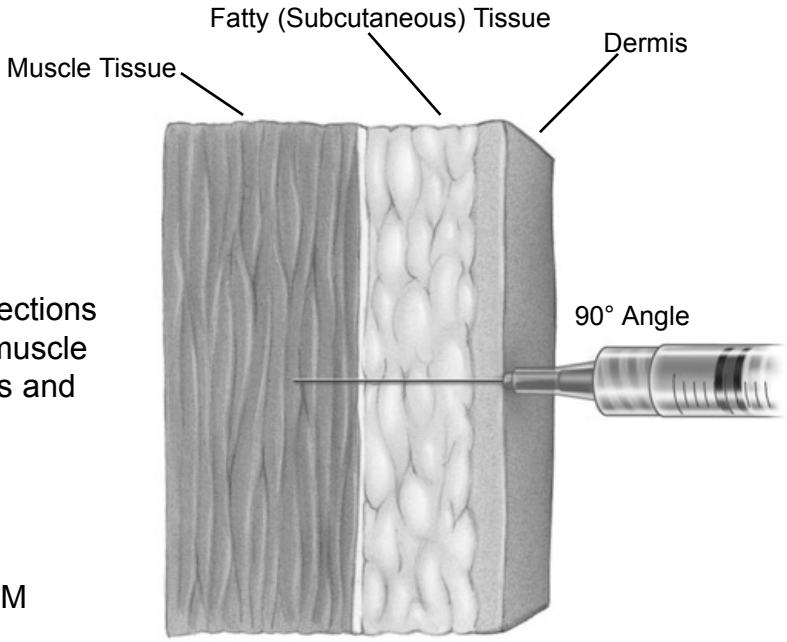
  - Follow standard medication administration guidelines for site assessment/selection and site preparation.

  - To avoid reaching the muscle, pinch up the fatty tissue, insert the needle at a 45° angle and inject the vaccine into the tissue.

  - Withdraw the needle and apply light pressure to the injection site for several seconds with a dry cotton ball or gauze.



Subcutaneous Administration Techniques



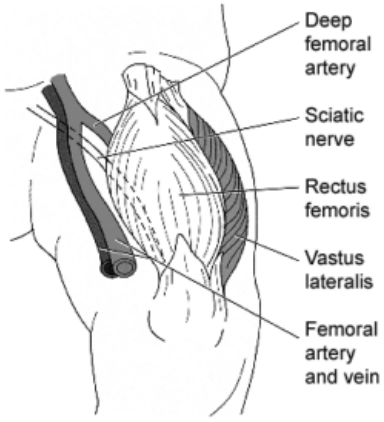
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- **Intramuscular** (IM) injections are administered into muscle tissue below the dermis and subcutaneous tissue.

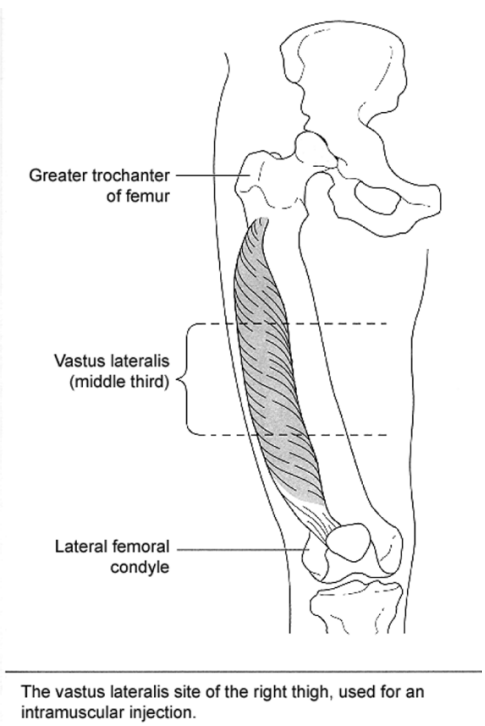
- **Site** - Although there are several IM injection sites on the body, the recommended IM sites for vaccine administration are the vastus lateralis muscle (anterolateral thigh) and the deltoid muscle (upper arm). The site depends on the age of the individual and the degree of muscle development.



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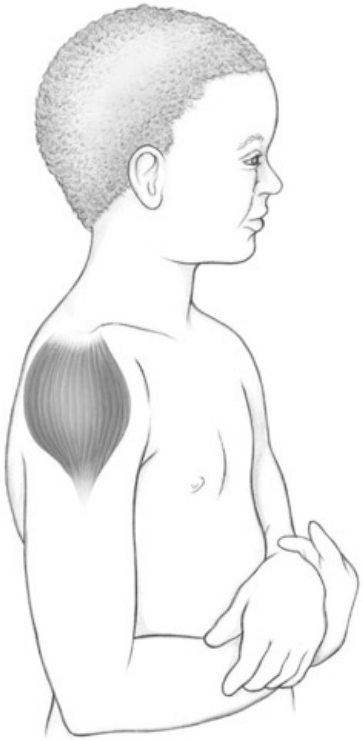


The vastus lateralis muscle of the upper thigh used for intramuscular injections.

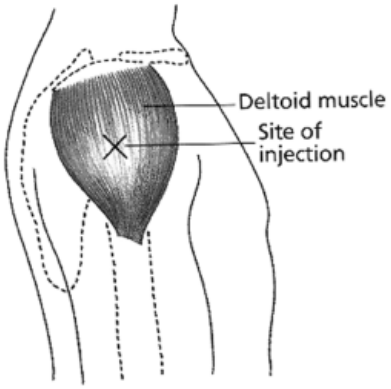


The vastus lateralis site of the right thigh, used for an intramuscular injection.

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- **Needle Gauge** - 22- to 25-gauge needle

- **Needle Length** - For all intramuscular injections, the needle should be long enough to reach the muscle mass and prevent vaccine from seeping into subcutaneous tissue, but not so long as to involve underlying nerves, blood vessels, or bone. The vaccinator should be familiar with the anatomy of the area into which the vaccine will be injected.

  Decision on needle size and site of injection must be made for each person on the basis of the size of the muscle, the thickness of adipose tissue at the injection site, the volume of the material to be administered, injection technique, and the depth below the muscle surface into which the material is to be injected

  - *Infants (Younger Than 12 Months)*
    For the majority of infants, the anterolateral aspect of the thigh is the recommended site for injection because it provides a large muscle mass. The muscles of the buttock have not been used for administration of vaccines in infants and children because of concern about potential injury to the sciatic nerve, which is well documented after injection of antimicrobial agents into the buttock. If the gluteal muscle must be used, care should be taken to define the anatomic landmarks.*

*If the gluteal muscle is chosen, injection should be administered lateral and superior to a line between the posterior superior iliac spine and the greater trochanter or in the ventrogluteal site, the center of a triangle bounded by the anterior superior iliac spine, the tubercle of the iliac crest, and the upper border of the greater trochanter.

Injection technique is the most important factor to ensure efficient intramuscular vaccine delivery. If the subcutaneous and muscle tissue are bunched to minimize the chance of striking bone, a 1-inch needle is required to ensure intramuscular administration in infants. For the majority of infants, a 1-inch, 22-25-gauge needle is sufficient to penetrate muscle in an infant's thigh. For newborn (first 28 days of life) and premature infants, a 5/8 inch needle usually is adequate if the skin is stretched flat between thumb and forefinger and the needle inserted at a 90-degree angle to the skin.

- *Toddlers and Older Children (12 Months through 10 Years)*
  The deltoid muscle should be used if the muscle mass is adequate. The needle size for deltoid site injections can range from 22 to 25 gauge and from 5/8 to 1 inch on the basis of the size of the muscle and the thickness of adipose tissue at the injection site. A 5/8-inch needle is adequate only for the deltoid muscle and only if the skin is stretched flat between thumb and forefinger and the needle inserted at a 90° angle to the skin. For toddlers, the anterolateral thigh can be used, but the needle should be at least 1 inch in length.

- *Adolescents and Adults (11 Years or Older)*
  For adults and adolescents, the deltoid muscle is recommended for routine intramuscular vaccinations. The anterolateral thigh also can be used. For men and women weighing less than 130 lbs (60 kg) a 5/8-1-inch needle is sufficient to ensure intramuscular injection. For women weighing 130-200 lbs (60-90 kg) and men 130-260 lbs (60-118kg), a 1-1½-inch needle is needed. For women weighing more than 200 lbs (90 kg) or men weighing more than 260 lbs (118 kg), a 1½-inch needle is required.

- **Technique**

  - Follow standard medication administration guidelines for site assessment/selection and site preparation.

  - To avoid injection into subcutaneous tissue, spread the skin of the selected vaccine administration site taut between the thumb and forefinger, isolating the muscle. Another technique, acceptable mostly for pediatric and geriatric patients, is to grasp the tissue and "bunch up" the muscle.

  - Insert the needle fully into the muscle at a 90° angle and inject the vaccine into the tissue.

  - Withdraw the needle and apply light pressure to the injection site for several seconds with a dry cotton ball or gauze.





- **Aspiration** - Aspiration is the process of pulling back on the plunger of the syringe prior to injection to ensure that the medication is not injected into a blood vessel. Although this practice is advocated by some experts, the procedure is not required because no large blood vessels exist at the recommended injection sites.

- **Multiple Vaccinations** - When administering multiple vaccines, NEVER mix vaccines in the same syringe unless approved for mixing by the Food and Drug Administration (FDA). If more than one vaccine must be administered in the same limb, the injection sites should be separated by 1-2 inches so that any local reactions can be differentiated. Vaccine doses range from 0.2 mL to 1 mL. The recommended maximum volume of medication for an IM site, varies among references and depends on the muscle mass of the individual. However, administering two IM vaccines into the same muscle would not exceed any suggested volume ranges for either the vastus lateralis or the deltoid muscle in any age group. The option to also administer a subcutaneous vaccine into the same limb, if necessary, is acceptable since a different tissue site is involved.

  If a vaccine and an immune globulin preparation are administered simultaneously (e.g., Td/Tdap and tetanus immune globulin [TIG] or hepatitis B vaccine and hepatitis B immune globulin [HBIG]), a separate anatomic site should be used for each injection. The location of each injection should be documented in the patient's medical record.

- **Nonstandard Administration** - Deviation from the recommended route, site and dosage of vaccine is strongly discouraged and can result in inadequate protection. In situations where nonstandard administration has occurred, refer to the ACIP General Recommendation on Immunization, *MMWR* 2006; 55 (RR-15), for specific guidance.

Special Situations

Bleeding Disorders - Individuals with a bleeding disorder or who are receiving anticoagulant therapy may develop hematomas in IM injection sites. Prior to administration of IM vaccines the patient or family should be instructed about the risk of hematoma formation from the injection. Additionally, a physician familiar with the patient's bleeding disorder or therapy should be consulted regarding the safety of administration by this route. If the patient periodically receives hemophilia replacement factor or other similar therapy, IM vaccine administration should ideally be scheduled shortly after replacement therapy. A 23-gauge or finer needle should be used and firm pressure applied to the site for at least 2 minutes. The site should not be rubbed or massaged.

Latex Allergy - Administration of a vaccine supplied in a vial or syringe that contains natural rubber (refer to product information) should not be administered to an individual with a history of a severe (anaphylactic) allergy to latex, unless the benefit of vaccination clearly outweighs the risk of an allergic reaction. These situations are rare. Medical consultation and direction should be sought regarding vaccination. A local or contact sensitivity to latex is not a contraindication to vaccination.

Syncopal or Vasovagal Response ("fainting") may occur during vaccine administration, especially with adolescents and adults. Because individuals may fall and sustain injury as a result, the provider should have the patient sit during injection(s). A syncopal or vasovagal response is not common and is not an allergic reaction. However, if syncope develops, the provider should observe and administer supportive care until the patient is recovered.

Anaphylaxis (a life-threatening acute allergic reaction) - Each facility that administers vaccines should have a protocol, procedures and equipment to provide initial care for suspected anaphylaxis. Facility staff should be prepared to recognize and respond appropriately to this type of emergency situation. All staff should maintain current CPR certification. Emergency protocols, procedures and equipment/supplies should be reviewed periodically. For additional information on medical management of vaccine reactions in children, teens, and adults, see the 2006 ACIP General Recommendations on Immunization (p. 19), the 2006 AAP *Red Book* (pp. 64-66), and pages D18-D21 of this appendix. Although both fainting and allergic reactions are rare, vaccine providers should strongly consider observing patients for 15 minutes after they are vaccinated.

Documentation

All vaccines administered should be fully documented in the patient's permanent medical record. Documentation should include:

1. Date of administration
2. Name or common abbreviation of vaccine
3. Vaccine lot number

4. Vaccine manufacturer

5. Administration site

6. Vaccine Information Statement (VIS) edition date (found in the lower right corner of the back of the VIS).

7. Name and address of vaccine administrator. This should be the address where the record is kept. If immunizations are given in a shopping mall, for example, the address would be the clinic where the permanent record will reside.

Facilities that administer vaccines are encouraged to participate in state/local immunization information systems. The patient or parent should be provided with an immunization record that includes the vaccines administered with dates of administration.

The California Department of Health Services' Immunization Branch has developed a complete package of resources on vaccine administration, including a training video, posters and a skills checklist.

Ordering information is available on the Immunization Action Coalition (IAC) website: www.immunize.org/iztech/index.htm

IMM-694B (9/01)

Skills Checklist for Immunization

The Skills Checklist is a self-assessment tool for health care staff who administer immunizations. To complete it, review the competency areas below and the clinical skills, techniques and procedures outlined for each of them. Score yourself in the Self-Assessment column. If you check **Need to Improve** you indicate further study, practice or change is needed. When you check **Meets or Exceeds** you indicate you believe you are performing at the expected level of competence, or higher.

Supervisors: Use the Skills Checklist to clarify responsibilities and expectations for staff who administer vaccines. When you use it for performance reviews, give staff the opportunity to score themselves in advance. Next observe their performance as they provide immunizations to several patients and score in the Supervisor Review columns. If improvement is needed, meet with them to develop a Plan of Action (over) that will help them achieve the level of competence you expect; circle desired actions or write in others. In 30 days, observe their performance again. When all competency areas meet expectations, file the Skills Checklist in their personnel folder. At the end of the probationary period and annually thereafter, observe them again and complete the Skills Checklist.

		Self-Assessment		Supervisor Review		
Competency	**Clinical Skills, Techniques, and Procedures**	**Need to Improve**	**Meets or Exceeds**	**Need to Improve**	**Meets or Exceeds**	**Plan of Action***
A. Patient/Parent Education	1. Welcomes patient/family, establishes rapport, and answers any questions.					
	2. Explains what vaccines will be given and which type(s) of injection will be done.					
	3. Accommodates language or literacy barriers and special needs of patient/parents to help make them feel comfortable and informed about the procedure.					
	4. Verifies patient/parents received the Vaccine Information Statements for indicated vaccines and had time to read them and ask questions.					
	5. Screens for contraindications. (MA: score NA–not applicable–if this is MD function.)					
	6. Reviews comfort measures and after care instructions with patient/parents, inviting questions.					
B. Medical Protocols	1. Identifies the location of the medical protocols (i.e. immunization protocol, emergency protocol, reference material).					
	2. Identifies the location of the epinephrine, its administration technique, and clinical situations where its use would be indicated.					
	3. Maintains up-to-date CPR certification.					
	4. Understands the need to report any needlestick injury and to maintain a sharps injury log.					
C. Vaccine Handling	1. Checks vial expiration date. Double-checks vial label and contents prior to drawing up.					
	2. Maintains aseptic technique throughout.					
	3. Selects the correct needle size. 1"-1 1/2" for IM (DTaP, Td, Hib, HepA, HepB, Pneumo Conj., Flu); 5/8" for SC (MMR, Var); IPV and Pneumo Poly depends on route to be used.					
	4. Shakes vaccine vial and/or reconstitutes and mixes using the diluent supplied. Inverts vial and draws up correct dose of vaccine. Rechecks vial label.					
	5. Labels each filled syringe or uses labeled tray to keep them identified.					
	6. Demonstrates knowledge of proper vaccine handling, e.g. protects MMR from light, logs refrigerator temperature.					

		Self-Assessment		Supervisor Review		
Competency	**Clinical Skills, Techniques, and Procedures**	**Need to Improve**	**Meets or Exceeds**	**Need to Improve**	**Meets or Exceeds**	**Plan of Action***
D. Administering Immunizations	1. Rechecks the physician's order or instructions against prepared syringes.					
	2. Washes hands and if office policy puts on disposable gloves.					
	3. Demonstrates knowledge of the appropriate route for each vaccine. (IM for DTaP, Td, Hib, HepA, HepB, Pneumo Conj, Flu; SC for MMR, Var; Either SC or IM for IPV and Pneumo Poly).					
	4. Positions patient and/or restrains the child with parent's help; locates anatomic landmarks specific for IM or SC					
	5. Preps the site with an alcohol wipe using a circular motion from the center to a 2" to 3" circle. Allows alcohol to dry.					
	6. Controls the limb with the non-dominant hand; holds the needle an inch from the skin and inserts it quickly at the appropriate angle (45° for SC or 90° for IM).					
	7. Injects vaccine using steady pressure; withdraws needle at angle of insertion.					
	8. Applies gentle pressure to injection site for several seconds with a dry cotton ball.					
	9. Properly disposes of needle and syringe in sharps container. Properly disposes of live vaccine vial.					
	10. Encourages comfort measures before, during and after the procedure.					
E. Records Procedures	1. Fully documents each immunization in patient's chart: date, lot number, manufacturer, site, VIS date, name/initials.					
	2. If applicable, demonstrates ability to use IZ registry or computer to call up patient record, assess what is due today, and update computer immunization history.					
	3. Asks for and updates patient's record of immunizations and reminds them to bring it to each visit.					

Plan of Action: **Circle desired next steps and write in the agreed deadline and date for the follow-up performance review.** **a.** Watch video on immunization techniques. **b.** Review office protocols. **c.** Review manuals, textbooks, wall charts or other guides. **d.** Review package inserts. **e.** Review vaccine handling guidelines or video. **f.** Observe other staff with patients. **g.** Practice injections. **h.** Read Vaccine Information Statements. **i.** Be mentored by someone who has these skills. **j.** Role play with other staff interactions with parents and patients, including age-appropriate comfort measures. **k.** Attend a skills training or other courses or training. **l.** Attend health care customer satisfaction or cultural competency training. **m.** Renew CPR certification. **Other:**_____

Employee Signature _____ Date _____

Supervisor Signature _____ Date _____

Plan of Action Deadline _____

Date of Next Performance Review _____

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IMM-694B (9/01)

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).



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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).



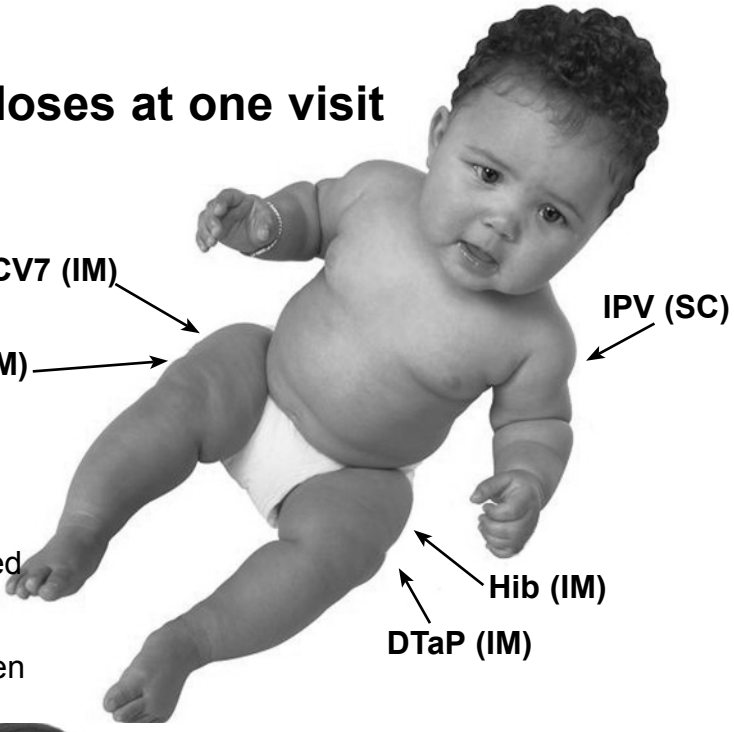
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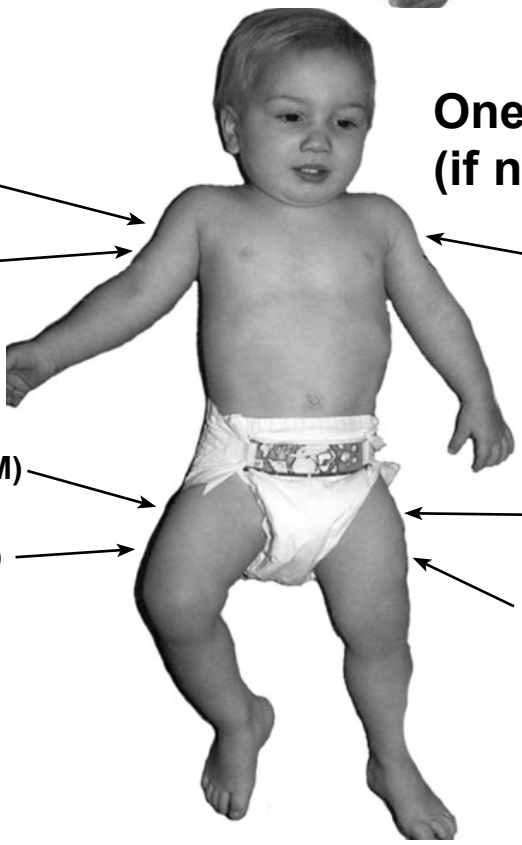
Giving All The Doses

One way to give 5 doses at one visit



- Injection sites should be separated by 1 inch
- IM injections not recommended in infant's arms
- SC injections can also be given

One way to give 7 doses (if needed) at one visit



The deltoid muscle is an option for IM injections in children 18 months and older with adequate muscle mass.

Medical Management of Vaccine Reactions in Children and Teens

All vaccines have the potential to cause an adverse reaction. To minimize adverse reactions, patients should be carefully screened for precautions and contraindications before vaccine is administered. Even with careful screening, reactions can occur. These reactions can vary from trivial and inconvenient (e.g., soreness, itching) to severe and life threatening (e.g., anaphylaxis). If reactions occur, staff should be prepared with procedures for their management. The table below describes procedures to follow if various reactions occur.

Reaction	Symptoms	Management
Localized	Soreness, redness, itching, or swelling at the injection site	Apply a cold compress to the injection site. Consider giving an analgesic (pain reliever) or antipruritic (anti-itch) medication.
	Slight bleeding	Apply an adhesive compress over the injection site.
	Continuous bleeding	Place thick layer of gauze pads over site and maintain direct and firm pressure; raise the bleeding injection site (e.g., arm) above the level of the patient's heart.
Psychological fright and syncope (fainting)	Fright before injection is given	Have patient sit or lie down for the vaccination.
	Extreme paleness, sweating, coldness of the hands and feet, nausea, light-headedness, dizziness, weakness, or visual disturbances	Have patient lie flat or sit with head between knees for several minutes. Loosen any tight clothing and maintain an open airway. Apply cool, damp cloths to patient's face and neck.
	Fall, without loss of consciousness	Examine the patient to determine if injury is present before attempting to move the patient. Place patient flat on back with feet elevated.
	Loss of consciousness	Check the patient to determine if injury is present before attempting to move the patient. Place patient flat on back with feet elevated. Call 911 if patient does not recover immediately.
Anaphylaxis	Sudden or gradual onset of generalized itching, erythema (redness), or urticaria (hives); angioedema (swelling of the lips, face, or throat); severe bronchospasm (wheezing); shortness of breath; shock; abdominal cramping; or cardiovascular collapse	See "Emergency Medical Protocol for Management of Anaphylactic Reactions in Children and Teens" on the next page for detailed steps to follow in treating anaphylaxis.

Supplies Needed

- ☐ Aqueous epinephrine 1:1000 dilution, in ampules, vials of solution, or prefilled syringes, including epinephrine auto-injectors (e.g., EpiPen). If EpiPens are to be stocked, both EpiPen Jr. (0.15 mg) and adult EpiPens (0.30 mg) should be available.
- ☐ Diphenhydramine (Benadryl) injectable (50 mg/mL solution) and oral (12.5 mg/5 mL suspension) and 25 mg or 50 mg capsules or tablets
- ☐ Syringes: 1–3 cc, 22–25g, 1", 1½", and 2" needles for epinephrine and diphenhydramine (Benadryl)
- ☐ Pediatric & adult airways (small, medium, and large)
- ☐ Sphygmomanometer (child, adult & extra-large cuffs) and stethoscope
- ☐ Pediatric & adult size pocket masks with one-way valve
- ☐ Alcohol swabs
- ☐ Tongue depressors
- ☐ Flashlight with extra batteries (for examination of mouth and throat)
- ☐ Wrist watch
- ☐ Tourniquet
- ☐ Cell phone or access to an on-site phone

(Page 1 of 2)

www.immunize.org/catg.d/p3082a.pdf • Item #P3082a (8/06)

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Emergency Medical Protocol for Management of Anaphylactic Reactions in Children and Teens

Signs and Symptoms of Anaphylactic Reaction

Sudden or gradual onset of generalized itching, erythema (redness), or urticaria (hives); angioedema (swelling of the lips, face, or throat); bronchospasm (wheezing); shortness of breath; shock; abdominal cramping; or cardiovascular collapse.

Treatment in Children and Teens

a. If itching and swelling are confined to the injection site where the vaccination was given, observe patient closely for the development of generalized symptoms.

b. If symptoms are generalized, activate the emergency medical system (EMS; e.g., call 911) and notify the on-call physician. This should be done by a second person, while the primary nurse assesses the airway, breathing, circulation, and level of consciousness of the patient.

c. Administer aqueous epinephrine 1:1000 dilution (i.e., 1 mg/mL) intramuscularly; the standard dose is 0.01 mg/kg body weight, up to 0.3 mg maximum single dose in children and 0.5 mg maximum in adolescents (see chart below).

d. In addition, for anaphylaxis, administer diphenhydramine either orally or by intramuscular injection; the standard dose is 1 mg/kg body weight, up to 30 mg maximum dose in children and 100 mg maximum dose in adolescents (see chart below).

e. Monitor the patient closely until EMS arrives. Perform cardiopulmonary resuscitation (CPR), if necessary, and maintain airway. Keep patient in supine position (flat on back) unless he or she is having breathing difficulty. If breathing is difficult, patient's head may be elevated, provided blood pressure is adequate to prevent loss of consciousness. If blood pressure is low, elevate legs. Monitor blood pressure and pulse every 5 minutes.

f. If EMS has not arrived and symptoms are still present, repeat dose of epinephrine every 10–20 minutes for up to 3 doses, depending on patient's response.

g. Record all vital signs, medications administered to the patient, including the time, dosage, response, and the name of the medical personnel who administered the medication, and other relevant clinical information.

h. Notify the patient's primary care physician.

Suggested Dosing of Epinephrine and Diphenhydramine

Age Group Dose	**Weight * in kg**	**Weight (lbs)* in lbs**	**Epinephrine Dose** 1 mg/mL injectable (1:1000 dilution) intramuscular	**Diphenhydramine (Benadryl)** 12.5 mg/5 mL liquid 25 and 50 mg capsules or tabs 50 mg/mL injectable
1–6 mos	4–7 kg	9–15 lbs	0.05 mg (0.05 ml)	5 mg
7–18 mos	7–11 kg	15–24 lbs	0.1 mg (0.1 ml)	10 mg
19–36 mos	11–14 kg	24–31 lbs	0.15 mg (0.15 ml)	15 mg
37–48 mos	14–17 kg	31–37 lbs	0.15 mg (0.15 ml)	20 mg
49–59 mos	17–19 kg	37–42 lbs	0.2 mg (0.2 ml)	
5–7 yrs	19–23 kg	42–51 lbs	0.2 mg (0.2 ml)	30 mg
8–10 yrs	23–35 kg	51–77 lbs	0.3 mg (0.3 ml)	
11–12 yrs	35–45 kg	77–99 lbs	0.4 mg (0.4 ml)	40 mg
13 yrs & older	45+ kg	99+ lbs	0.5 mg (0.5 ml)	50–100 mg

*Dosing by body weight is preferred.

These standing orders for the medical management of vaccine reactions in child and teenage patients shall remain in effect for patients of the _____ (*name of clinic*) until rescinded or until _____ (*date*).

Medical Director's signature _____ Effective date _____

Sources: American Academy of Pediatrics. Passive Immunization. In: Pickering LK, ed. *Red Book: 2006 Report of the Committee on Infectious Diseases.* 27th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2006: 64–66.

American Pharmacists Association, Grabenstein, JD, *Pharmacy-Based Immunization Delivery,* 2002.

Medical Management of Vaccine Reactions in Adult Patients

All vaccines have the potential to cause an adverse reaction. In order to minimize adverse reactions, patients should be carefully screened for precautions and contraindications before vaccine is administered. Even with careful screening, reactions may occur. These reactions can vary from trivial and inconvenient (e.g., soreness, itching) to severe and life threatening (e.g., anaphylaxis). If reactions occur, staff should be prepared with procedures for their management. The table below describes procedures to follow if various reactions occur.

Reaction	Symptoms	Management
Localized	Soreness, redness, itching, or swelling at the injection site	Apply a cold compress to the injection site. Consider giving an analgesic (pain reliever) or antipruritic (anti-itch) medication.
	Slight bleeding	Apply an adhesive compress over the injection site.
	Continuous bleeding	Place thick layer of gauze pads over site and maintain direct and firm pressure; raise the bleeding injection site (e.g., arm) above the level of the patient's heart.
Psychological fright and syncope (fainting)	Fright before injection is given	Have patient sit or lie down for the vaccination.
	Extreme paleness, sweating, coldness of the hands and feet, nausea, light-headedness, dizziness, weakness, or visual disturbances	Have patient lie flat or sit with head between knees for several minutes. Loosen any tight clothing and maintain an open airway. Apply cool, damp cloths to patient's face and neck.
	Fall, without loss of consciousness	Examine the patient to determine if injury is present before attempting to move the patient. Place patient flat on back with feet elevated.
	Loss of consciousness	Check the patient to determine if injury is present before attempting to move the patient. Place patient flat on back with feet elevated. Call 911 if patient does not recover immediately.
Anaphylaxis	Sudden or gradual onset of generalized itching, erythema (redness), or urticaria (hives); angioedema (swelling of the lips, face, or throat); severe bronchospasm (wheezing); shortness of breath; shock; abdominal cramping; or cardiovascular collapse.	See "Emergency Medical Protocol for Management of Anaphylactic Reactions in Adults" on the next page for detailed steps to follow in treating anaphylaxis.

(continued on page 2)

Technical content reviewed by the Centers for Disease Control and Prevention, Nov. 2006. www.immunize.org/catg.d/p3082.pdf • Item #P3082 (11/06)

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(continued from page 1)

Emergency Medical Protocol for Management of Anaphylactic Reactions in Adults

Supplies Needed

- ☐ Aqueous epinephrine 1:1000 (i.e., 1 mg/mL) dilution, in ampules, vials of solution, or prefilled syringes, including epinephrine autoinjectors (e.g., EpiPen). If EpiPens are stocked, at least three adult EpiPens (0.30 mg) should be available.
- ☐ Diphenhydramine (Benadryl) injectable (50 mg/mL solution) and 25 mg or 50 mg capsules or tablets and syrup (12.5 mg/5 mL suspension)
- ☐ Syringes: 1–3 cc, 22–25g, 1", 1½", and 2" needles for epinephrine and diphenhydramine (Benadryl)
- ☐ Wristwatch with second hand
- ☐ Adult airways (small, medium, and large)
- ☐ Sphygmomanometer (adult and extra-large cuffs) and stethoscope
- ☐ Adult size pocket mask with one-way valve
- ☐ Alcohol swabs
- ☐ Tourniquet
- ☐ Tongue depressors
- ☐ Flashlight with extra batteries (for examination of the mouth and throat)
- ☐ Cell phone or access to an on-site phone

Signs and Symptoms of Anaphylactic Reaction

Sudden or gradual onset of generalized itching, erythema (redness), or urticaria (hives); angioedema (swelling of the lips,face, or throat); bronchospasm (wheezing); shortness of breath; shock; abdominal cramping; or cardiovascular collapse.

Treatment in Adults

a. If itching and swelling are confined to the injection site where the vaccination was given, observe patient closely for the development of generalized symptoms.

b. If symptoms are generalized, activate the emergency medical system (EMS; e.g., call 911) and notify the on-call physician. This should be done by a second person, while the primary nurse assesses the airway, breathing, circulation, and level of consciousness of the patient.

c. Administer aqueous epinephrine 1:1000 dilution intramuscularly, 0.01 mL/kg/dose (adult dose ranges from 0.3 mL to 0.5 mL, with maximum single dose of 0.5 mL).

d. In addition, for systemic anaphylaxis, administer diphenhydramine either orally or by intramuscular injection; the standard dose is 1–2 mg/kg, up to 100 mg maximum single dose.

e. Monitor the patient closely until EMS arrives. Perform cardiopulmonary resuscitation (CPR), if necessary, and maintain airway. Keep patient in supine position (flat on back) unless he or she is having breathing difficulty. If breathing is difficult, patient's head may be elevated, provided blood pressure is adequate to prevent loss of consciousness. If blood pressure is low, elevate legs. Monitor blood pressure and pulse every 5 minutes.

f. If EMS has not arrived and symptoms are still present, repeat dose of epinephrine every 10–20 minutes for up to 3 doses, depending on patient's response.

g. Record all vital signs, medications administered to the patient, including the time, dosage, response, and the name of the medical personnel who administered the medication, and other relevant clinical information.

h. Notify the patient's primary care physician.

Sources: 1. American Academy of Pediatrics. Passive Immunization. In: Pickering LK, ed. *Red Book: 2006 Report of the Committee on Infectious Diseases.* 27th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2006:64–66.
2. American Pharmacists Association, Grabenstein, JD, *Pharmacy-Based Immunization Delivery,* 2002.
3. *Got Your Shots? A Providers Guide to Immunizations in Minnesota,* Second Edition, Minnesota Department of Health, 2001:80-82.

These standing orders for the medical management of vaccine reactions in adult patients shall remain in effect for patients of the _____ (*name of clinic*) until rescinded or until _____ (*date*).

_____ Medical Director's signature

_____ Effective date

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.

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Grantland Johnson, Secretary—Health and Human Services Agency
Diana M. Bontá, R.N., Dr.P.H., Director—Department of Health Services
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dhs
IMM-720 (12/01)

APPENDIX E

Vaccine Information Statements

It's Federal Law **E-1**

Instructions for Use of VISs **E-2**

How to Get Vaccine Information Statements **E-3**

VIS Questions and Answers **E-4**

CDC's Vaccine Information Statement Webpage **E-8**

Appendix E

It's federal law!

You must give your patients current Vaccine Information Statements (VISs)

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), 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.*

To obtain a complete set of current VISs in up to 30 languages, visit IAC's website at www.immunize.org/vis.

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 November 2006.

As healthcare professionals 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 vaccine recipients (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 healthcare providers and vaccines. Vaccine Information Statements (VISs) provide a standardized way to present objective information about vaccine benefits and adverse events.

What are VISs?

VISs are developed by the staff of the Centers for Disease Control and Prevention (CDC) and undergo intense scrutiny by panels of experts for accuracy. Each VIS provides information to properly inform the adult vaccine recipient or the minor child's parent or legal representative about the risks and benefits of each vaccine. VISs are not meant to replace interactions with healthcare providers who should answer questions and address concerns that the recipient or the parent/legal representative may have.

Use of the VIS is mandatory!

Before a healthcare provider vaccinates a child or an adult with a dose of any vaccine containing diphtheria, tetanus, pertussis, measles, mumps, rubella, polio, hepatitis A, hepatitis B, *Haemophilus influenzae* type b (Hib), varicella (chickenpox), influenza, 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 recipient or to the child's parent/legal representative.

VISs are also available for human papillomavirus (HPV), meningococcal, pneumococcal polysaccharide, and rotavirus, as well as various vaccines used primarily for international travelers. The use of these VISs is recommended but not currently required by federal law. (Editor's note: Use of VISs for HPV, meningococcal, and rotavirus vaccines will become mandatory at a later date.)

State or local health departments or individual providers may place the clinic name on the VISs, but any other changes must be approved by the director of CDC's National Center for Immunization and Respiratory Diseases.

What to do with VISs

Some of the legal requirements concerning the use of VISs are as follows:

1. Before an NCVIA-covered vaccine is administered to anyone (this includes adults!), you must give the patient or the parent/legal representative a copy of the most current VIS available for that vaccine. Make sure you give your patient time to read the VIS prior to the administration of the vaccine.
2. You must record in your patient's chart the date the VIS was given.
3. You must also record on the patient's chart the publication date of the VIS, which appears on the bottom of the VIS. As the Florida case above illustrates, it is imperative that you have the most current VIS.

Most current versions of VISs

As of November 2006, the most recent versions of the VISs are as follows:

DTaP/DT/DTP 7/30/01	PCV 9/30/02
hepatitis A 3/21/06	PPV 7/29/97
hepatitis B 7/11/01	polio 1/1/00
HPV (H. papillomavirus) 9/5/06	rabies 1/12/06
Hib 12/16/98	rotavirus 4/12/06
influenza (LAIV) ... 6/30/06	shingles 9/11/06
influenza (TIV) 6/30/06	Td 6/10/94
Japan. enceph. ... 5/11/05	Tdap 7/12/06
meningococcal 10/7/05	typhoid 5/19/04
MMR 1/15/03	varicella 12/16/98
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 VISs in more than 30 languages on the Immunization Action Coalition's website at www.immunize.org/vis.

"We have an obligation to provide patients and/or parents with information that includes both the benefits and the risks of vaccines. This can be done with the Vaccine Information Statements that healthcare providers are required by law to provide prior to the administration of vaccines."

Walter A. Orenstein, MD, past director, National Immunization Program, CDC

Technical content reviewed by the Centers for Disease Control and Prevention, Nov. 2006.

www.immunize.org/catg.d/p2027law.pdf • Item #P2027 (11/06)

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 A (use of hepatitis A VIS required effective July 1, 2006), hepatitis B, *Haemophilus influenzae* type b (Hib), trivalent influenza, 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 A: 3/21/06
Hepatitis B: 7/11/01
Inactivated Influenza: 6/30/06
Live, Intranasal Influenza: 6/30/06
Measles, Mumps, Rubella (MMR): 1/15/03
Pneumococcal conjugate: 9/30/02
Polio: 1/1/00
Tetanus Diphtheria (Td): 6/10/94
Varicella (chickenpox): 1/10/07

Reference 42 U.S.C. §300aa-26

1/17/07

CDC

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.

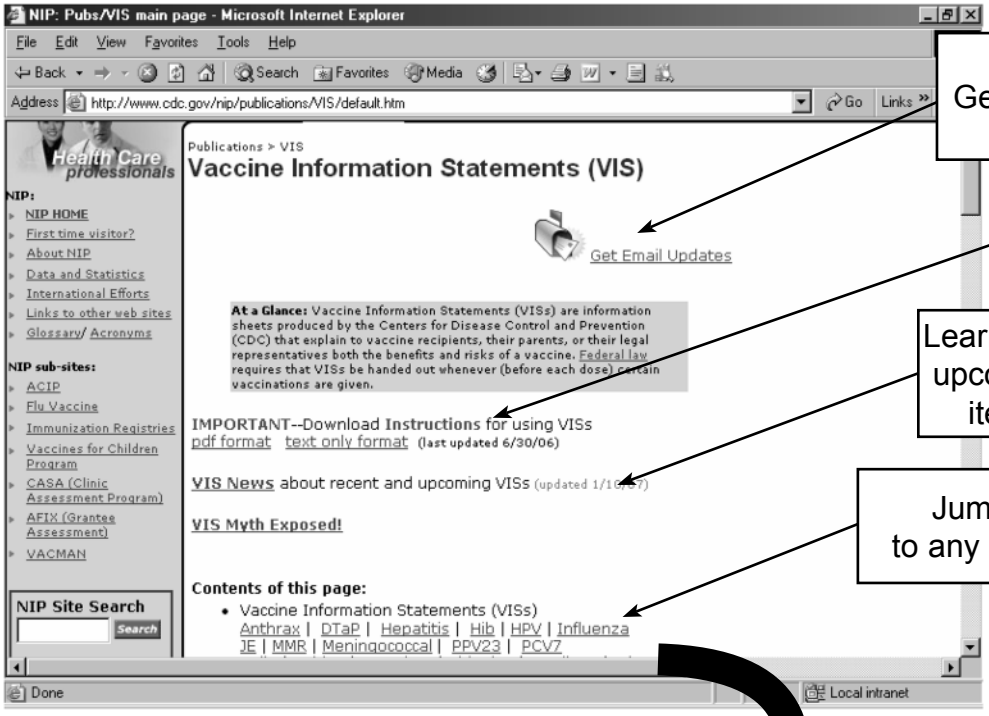
The program must maintain the original consent signature and any additional dose veto statements in the patient's medical record. A record must be kept of the dates prior to additional doses that the VIS was mailed, or sent home with the adolescent.

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

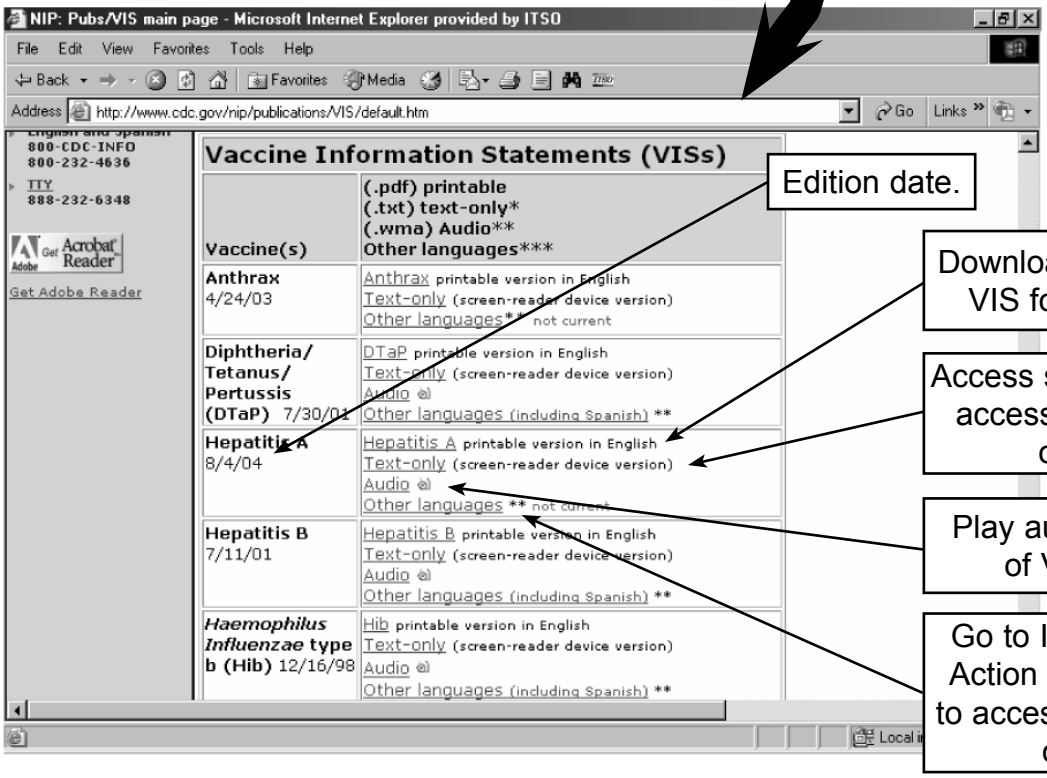


NEW
Get on mailing list for VIS updates.

Download VIS Instructions

Learn about new VISs, upcoming VISs, other items of interest.

Jump to any VIS.



Edition date.

Download pdf file of VIS for printing.

Access screenreader-accessible version of VIS.

Play audio file of VIS.

Go to Immunization Action Coalition site to access translations of VIS.

APPENDIX F

Vaccine Safety

The Vaccine Adverse Event Reporting System (VAERS) F-1

Table of Reportable Events Following Vaccination F-2

Vaccine Adverse Event Reporting System (VAERS) Form F-4

The Vaccine Injury Compensation Program (VICP) F-6

The VICP Vaccine Injury Table F-7

"Qualifications and Aids to Interpretation of Vaccine Injury Table" F-8

Appendix F

The Vaccine Adverse Event Reporting System (VAERS)

VAERS is a national vaccine safety surveillance program co-sponsored by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA). VAERS collects and analyzes information from reports of adverse events following immunization. Since 1990, VAERS has received over 123,000 reports, most of which describe mild side effects such as fever. Very rarely, people experience serious adverse events following immunization. By monitoring such events, VAERS can help to identify important new safety concerns.

Reporting to VAERS

Who can file a VAERS report: Anyone can submit a VAERS report. Most reports are sent in by vaccine manufacturers (42%) and health care providers (30%). The rest are submitted by state immunization programs (12%), vaccine recipients or their parent/guardians (7%), and other sources (9%).

What adverse events should be reported: VAERS encourages the reporting of any clinically significant adverse event that occurs after the administration of any vaccine licensed in the United States. Report such events even if you are unsure whether a vaccine caused them.

The National Childhood Vaccine Injury Act (NCVIA) requires health care providers to report:

- Any event listed by the vaccine manufacturer as a contraindication to subsequent doses of the vaccine.
- Any event listed in the Reportable Events Table that occurs within the specified time period after vaccination.

A copy of the Reportable Events Table can be found on the next page (F-2), or obtained by calling VAERS at 1-800-822-7967 or by downloading it from http://vaers.hhs.gov/pubs.htm.

Filing a VAERS report: Use a VAERS report form (see page F-4) to report any adverse event. You can get pre-addressed postage paid report forms by calling VAERS at 1-800-822-7967, or download a printable copy of the VAERS form from the following Internet sites:

- The VAERS Web site at http://vaers.hhs.gov/
- The Food and Drug Administration's Web site at 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).

Appendix F

VAERS Table of Reportable Events Following Vaccination*

Vaccine/Toxoid	Event	Interval from Vaccination
Tetanus in any combination; DTaP, DTP, DTP-HiB, DT, Td, TT, Tdap	A. Anaphylaxis or anaphylactic shock B. Brachial neuritis C. Any acute complications or sequela (including death) of above events D. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	7 days 28 days Not applicable See package insert
Pertussis in any combination; DTaP, DTP, DTP-HiB, P, Tdap	A. Anaphylaxis or anaphylactic shock B. Encephalopathy (or encephalitis) C. Any acute complications or sequela (including death) of above events D. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	7 days 7 days Not applicable See package insert
Measles, mumps and rubella in any combination; MMR, MR, M, MMRV, R	A. Anaphylaxis or anaphylactic shock B. Encephalopathy (or encephalitis) C. Any acute complications or sequela (including death) of above events D. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	7 days 15 days Not applicable See package insert
Rubella in any combination; MMR, MMRV, MR, R	A. Chronic arthritis B. Any acute complications or sequela (including death) of above event C. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	42 days Not applicable See package insert
Measles in any combination; MMR, MMRV, MR, M	A. Thrombocytopenic purpura B. Vaccine-strain measles viral infection in an immunodeficient recipient C. Any acute complications or sequela (including death) of above events D. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	7-30 days 6 months Not applicable See package insert
Oral Polio (OPV)	A. Paralytic polio – in a non-immunodeficient recipient – in an immunodeficient recipient – in a vaccine associated community case B. Vaccine-strain polio viral infection – in a non-immunodeficient recipient – in an immunodeficient recipient – in a vaccine associated community case C. Any sequela (including death) of above events D. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	 30 days 6 months Not applicable 30 days 6 months Not applicable Not applicable See package insert
Inactivated Polio (IPV)	A. Anaphylaxis or anaphylactic shock B. Any sequela (including death) of the above event C. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	7 days Not applicable See package insert
Hepatitis B	A. Anaphylaxis or anaphylactic shock B. Any acute complications or sequela (including death) of the above event C. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	7 days Not applicable See package insert
Hemophilus influenzae type b (conjugate)	A. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert
Varicella	A. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert
Rotavirus	A. Intussusception B. Any acute complications or sequela (including death) of the above event C. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	30 days Not applicable See package insert
Pneumococcal conjugate	A. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert
Hepatitis A	A. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert
Influenza	A. Events described in manufacturer's package insert as contraindications to additional doses of vaccine	See package insert

* **Effective date: July 01, 2005.** The Reportable Events Table (RET) reflects what is reportable by law (42 USC 300aa-25) to the Vaccine Adverse Event Reporting System (VAERS) including conditions found in the manufacturers package insert. In addition, individuals are encouraged to report **any** clinically significant or unexpected events (even if you are not certain the vaccine caused the event) for **any** vaccine, whether or not it is listed on the RET. Manufacturers are also required by regulation (21CFR 600.80) to report to the VAERS program all adverse events made known to them for any vaccine.

Reportable Events Table Definitions

Anaphylaxis and anaphylactic shock. Anaphylaxis and anaphylactic shock mean an acute, severe, and potentially lethal systemic allergic reaction. Most cases resolve without sequelae. Signs and symptoms begin minutes to a few hours after exposure. Death, if it occurs, usually results from airway obstruction caused by laryngeal edema or bronchospasm and may be associated with cardiovascular collapse.

Brachial neuritis is defined as dysfunction limited to the upper extremity nerve plexus (i.e., its trunks, division, or cords) without involvement of other peripheral (e.g., nerve roots or a single peripheral nerve) or central (e.g., spinal cord) nervous system structures. A deep, steady, often severe aching pain in the shoulder and upper arm usually heralds onset of the condition. The pain is followed in days or weeks by weakness and atrophy in upper extremity muscle groups. Sensory loss may accompany the motor deficits, but is generally a less notable clinical feature.

Encephalopathy. For purposes of the Reportable Events Table, a vaccine recipient shall be considered to have suffered an encephalopathy only if such recipient manifests, within the applicable period, an injury meeting the description below of an acute encephalopathy, and then a chronic encephalopathy persists in such person for more than 6 months beyond the date of vaccination.

1. An ***acute encephalopathy*** is one that is sufficiently severe so as to require hospitalization (whether or not hospitalization occurred).
   a. For ***children less than 18 months of age*** who present without an associated seizure event, an acute encephalopathy is indicated by a "significantly decreased level of consciousness" (see "D" below) lasting for at least 24 hours. Those children less than 18 months of age who present following a seizure shall be viewed as having an acute encephalopathy if their significantly decreased level of consciousness persists beyond 24 hours and cannot be attributed to a postictal state (seizure) or medication.
   b. For adults and ***children 18 months of age*** or older, an acute encephalopathy is one that persists for at least 24 hours and is characterized by at least two of the following:
      i. A significant change in mental status that is not medication related: specifically a confusional state, or a delirium, or a psychosis;
      ii. A significantly decreased level of consciousness, which is independent of a seizure and cannot be attributed to the effects of medication; and
      iii. A seizure associated with loss of consciousness.
   c. Increased intracranial ***pressure*** may be a clinical feature of acute encephalopathy in any age group.
2. A "***significantly decreased level of consciousness***" is indicated by the presence of at least one of the following clinical signs for at least 24 hours or greater:
   a. Decreased or absent response to environment (responds, if at all, only to loud voice or painful stimuli);
   b. Decreased or absent eye contact (does not fix gaze upon family members or other individuals); or
   c. Inconsistent or absent responses to external stimuli (does not recognize familiar people or things).

   The following clinical features alone, or in combination, do not demonstrate an acute encephalopathy or a significant change in either mental status or level of consciousness as described above: Sleepiness, irritability (fussiness), high-pitched and unusual screaming, persistent inconsolable crying, and bulging fontanelle. Seizures in themselves are not sufficient to constitute a diagnosis of encephalopathy. In the absence of other evidence of an acute encephalopathy, seizures shall not be viewed as the first symptom or manifestation of the onset of an acute encephalopathy.
3. ***Chronic Encephalopathy*** occurs when a change in mental or neurologic status, first manifested during the applicable time period, persists for a period of at least 6 months from the date of vaccination. Individuals who return to a normal neurologic state after the acute encephalopathy shall not be presumed to have suffered residual neurologic damage from that event; any subsequent chronic encephalopathy shall not be presumed to be a sequela of the acute encephalopathy. If a preponderance of the evidence indicates that a child's chronic encephalopathy is secondary to genetic, prenatal or perinatal factors, that chronic encephalopathy shall not be considered to be a condition set forth in the Table.
   An encephalopathy shall not be considered to be a condition set forth in the Table if it is shown that the encephalopathy was caused by an infection, a toxin, a metabolic disturbance, a structural lesion, a genetic disorder or trauma (without regard to whether the cause of the infection, toxin, trauma, metabolic disturbance, structural lesion or genetic disorder is known).

Chronic Arthritis. For purposes of the Reportable Events Table, chronic arthritis may be found in a person with no history in the 3 years prior to vaccination of arthropathy (joint disease) on the basis of:

   a. Medical documentation, recorded within 30 days after the onset, of objective signs of acute arthritis (joint swelling) that occurred between 7 and 42 days after a rubella vaccination; and
   b. Medical documentation (recorded within 3 years after the onset of acute arthritis) of the persistence of objective signs of intermittent or continuous arthritis for more than 6 months following vaccination.
   c. Medical documentation of an antibody response to the rubella virus.

The following shall not be considered as chronic arthritis: Musculoskeletal disorders such as diffuse connective tissue diseases (including but not limited to rheumatoid arthritis, juvenile rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, mixed connective tissue disease, polymyositis/dermatomyositis, fibromyalgia, necrotizing vasculitis and vasculopathies and Sjogren's Syndrome), degenerative joint disease, infectious agents other than rubella (whether by direct invasion or as an immune reaction), metabolic and endocrine diseases, trauma, neoplasms, neuropathic disorders, bone and cartilage disorders and arthritis associated with ankylosing spondylitis, psoriasis, inflammatory bowel disease, Reiter's syndrome, or blood disorders.

Arthralgia (joint pain) or stiffness without joint swelling shall not be viewed as chronic arthritis.

Sequela. The term "sequela" means a condition or event, which was actually caused by a condition listed in the Reportable Events Table.

Appendix F

WEBSITE: www.vaers.hhs.gov E-MAIL: info@vaers.org FAX: 1-877-721-0366

VACCINE ADVERSE EVENT REPORTING SYSTEM
24 Hour Toll-Free Information 1-800-822-7967
P.O. Box 1100, Rockville, MD 20849-1100
PATIENT IDENTITY KEPT CONFIDENTIAL

VAERS

For CDC/FDA Use Only
VAERS Number _____
Date Received _____

Patient Name:
Last First M.I.
Address
City State Zip
Telephone no. (____) _____

Vaccine administered by (Name):
Responsible Physician _____
Facility Name/Address
City State Zip
Telephone no. (____) _____

Form completed by (Name):
Relation to Patient ☐ Vaccine Provider ☐ Patient/Parent ☐ Manufacturer ☐ Other
Address *(if different from patient or provider)*
City State Zip
Telephone no. (____) _____

1. State | 2. County where administered | 3. Date of birth mm / dd / yy | 4. Patient age | 5. Sex ☐ M ☐ F | 6. Date form completed mm / dd / yy

7. Describe adverse events(s) (symptoms, signs, time course) and treatment, if any

8. Check all appropriate:
☐ Patient died (date mm / dd / yy)
☐ Life threatening illness
☐ Required emergency room/doctor visit
☐ Required hospitalization (_____days)
☐ Resulted in prolongation of hospitalization
☐ Resulted in permanent disability
☐ None of the above

9. Patient recovered ☐ YES ☐ NO ☐ UNKNOWN

10. Date of vaccination mm / dd / yy Time _____ AM PM

11. Adverse event onset mm / dd / yy Time _____ AM PM

12. Relevant diagnostic tests/laboratory data

13. Enter all vaccines given on date listed in no. 10

	Vaccine (type)	Manufacturer	Lot number	Route/Site	No. Previous Doses
a.					
b.					
c.					
d.					

14. Any other vaccinations within 4 weeks prior to the date listed in no. 10

	Vaccine (type)	Manufacturer	Lot number	Route/Site	No. Previous doses	Date given
a.						
b.						

15. Vaccinated at:
☐ Private doctor's office/hospital ☐ Military clinic/hospital
☐ Public health clinic/hospital ☐ Other/unknown

16. Vaccine purchased with:
☐ Private funds ☐ Military funds
☐ Public funds ☐ Other/unknown

17. Other medications

18. Illness at time of vaccination (specify)

19. Pre-existing physician-diagnosed allergies, birth defects, medical conditions (specify)

20. Have you reported this adverse event previously? ☐ No ☐ To health department ☐ To doctor ☐ To manufacturer

Only for children 5 and under
22. Birth weight _____ lb. _____ oz.
23. No. of brothers and sisters

21. Adverse event following prior vaccination (check all applicable, specify)

	Adverse Event	Onset Age	Type Vaccine	Dose no. in series
☐ In patient				
☐ In brother or sister				

Only for reports submitted by manufacturer/immunization project
24. Mfr./imm. proj. report no.
25. Date received by mfr./imm.proj.
26. 15 day report? ☐ Yes ☐ No
27. Report type ☐ Initial ☐ Follow-Up

Health care providers and manufacturers are required by law (42 USC 300aa-25) to report reactions to vaccines listed in the Table of Reportable Events Following Immunization. Reports for reactions to other vaccines are voluntary except when required as a condition of immunization grant awards.

Form VAERS-1(FDA)

"Fold in thirds, tape & mail — DO NOT STAPLE FORM"

NO POSTAGE
NECESSARY
IF MAILED
IN THE
UNITED STATES
OR APO/FPO

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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 - F7).

The Claims Process

An individual claiming a vaccine-related injury or death files a petition for compensation with the Court, and may be represented by an attorney. The Secretary of HHS is named as the Respondent.

An HHS physician reviews the petition to determine whether it meets the medical criteria for compensation. This recommendation is provided to the Court through a Respondent's report filed by the DOJ. The HHS position is presented by an attorney from the DOJ in hearings before a "special master," who makes the decision for compensation under the VICP. A decision may be appealed to the Court, then to the Federal Circuit Court of Appeals, and eventually to the U.S. Supreme Court.

If a case is found eligible for compensation, the amount of the award is usually negotiated between the DOJ and the petitioner's attorneys. If the attorneys can't agree, the case is scheduled for a hearing for the special master to assess the amount of compensation. Compensable claims, and even most claims found to be non-compensable, are awarded reimbursement for attorney's fees and costs. A petitioner may file a claim in civil court against the vaccine company and/or the vaccine administrator only after first filing a claim under the VICP and then rejecting the decision of the Court.

For more information, including information about restrictions that apply to filing a petition, visit the VICP website at http://www.hrsa.gov/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).

Appendix F

Qualifications and Aids to Interpretation

(1) **Anaphylaxis and anaphylactic shock** mean an acute, severe, and potentially lethal systemic allergic reaction. Most cases resolve without sequelae. Signs and symptoms begin minutes to a few hours after exposure. Death, if it occurs, usually results from airway obstruction caused by laryngeal edema or bronchospasm and may be associated with cardiovascular collapse. Other significant clinical signs and symptoms may include the following: Cyanosis, hypotension, bradycardia, tachycardia, arrhythmia, edema of the pharynx and/or trachea and/or larynx with stridor and dyspnea. Autopsy findings may include acute emphysema which results from lower respiratory tract obstruction, edema of the hypopharynx, epiglottis, larynx, or trachea and minimal findings of eosinophilia in the liver, spleen and lungs. When death occurs within minutes of exposure and with out signs of respiratory distress, there may not be significant pathologic findings.

(2) **Encephalopathy**. For purposes of the Vaccine Injury Table, a vaccine recipient shall be considered to have suffered an encephalopathy only if such recipient manifests, within the applicable period, an injury meeting the description below of an acute encephalopathy, and then a chronic encephalopathy persists in such person for more than 6 months beyond the date of vaccination.

(i) An acute encephalopathy is one that is sufficiently severe so as to require hospitalization (whether or not hospitalization occurred).

(A) For children less than 18 months of age who present without an associated seizure event, an acute encephalopathy is indicated by a "significantly decreased level of consciousness" (see "D" below) lasting for at least 24 hours. Those children less than 18 months of age who present following a seizure shall be viewed as having an acute encephalopathy if their significantly decreased level of consciousness persists beyond 24 hours and cannot be attributed to a postictal state (seizure) or medication.

(B) For adults and children 18 months of age or older, an acute encephalopathy is one that persists for at 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 consider the entire medical record.

3) **Seizure and convulsion**. For purposes of paragraphs (b)(2) of this section, the terms, "seizure" and "convulsion" include myoclonic, generalized tonic-clonic (grand mal), and simple and complex partial seizures. Absence (petit mal) seizures shall not be considered to be a condition set forth in the Table. Jerking 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 infectio**n is defined as a disease caused by poliovirus that is isolated from the affected tissue and should be determined to be the vaccine-strain by oligonucleotide or polymerase chain reaction. Isolation of poliovirus from the stool is not sufficient to establish a tissue specific infection or disease caused by vaccine-strain poliovirus.

APPENDIX G

Data and Statistics

Reported Cases and Deaths from Vaccine-Preventable Diseases: 1950-2007* **G-1**
*Provisional

Impact of Vaccines in the 20th & 21st Centuries **G-7**

Vaccine Coverage Levels: 1962-2006 . . . . . **G-8**

Appendix G

Reported Cases and Deaths from Vaccine Preventable Diseases, United States, 1950-2007*

	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
1961	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

*2007 provisional data. *MMWR* 2007;56(Nos. 51&52):1360-69.

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	Diphtheria		Tetanus		Pertussis		Polio (paralytic)	
Year	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
1979	59	1	81	30	1,623	6	22	1
1980	3	1	95	28	1,730	11	9	2
1981	5	0	72	31	1,248	6	10	0
1982	2	1	88	22	1,895	4	12	0
1983	5	0	91	22	2,463	5	13	0
1984	1	0	74	20	2,276	7	9	0
1985	3	0	83	23	3,589	4	8	0
1986	0	0	64	22	4,195	6	10	0
1987	3	1	48	16	2,823	1	9	0
1988	2	0	53	17	3,450	4	9	0
1989	3	0	53	9	4,157	12	10	0
1990	4	1	64	11	4,570	12	6	0
1991	5	0	57	11	2,719	0	9	1
1992	4	1	45	9	4,083	5	6	0
1993	0	0	48	11	6,586	1	3	0
1994	2	0	51	9	4,617	8	8	0
1995	0	1	41	5	5,137	6	6	1
1996	2	0	36	1	7,796	4	7	0
1997	4	0	50	4	6,564	6	7	0
1998	1	1	34	7	6,279	5	2	0
1999	1	1	40	7	7,288	7	2	0
2000	1	0	35	5	7,867	12	0	0
2001	2	0	37	5	7,580	17	0	0
2002	1	0	25	5	9,771	18	0	0
2003	1	1	20	4	11,647	11	0	0
2004	0	NA	34	NA	25,827	NA	0	0
2005	0	NA	27	NA	25,616	NA	1**	0
2006	0	NA	41	NA	15,632	NA	0	0
2007*	0	NA	20	NA	8,739	NA	0	0

**vaccine-associated polio acquired outside the United States

	Measles		Mumps		Rubella		CRS
Year	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases
1950	319,124	468	NR		NR		NR
1951	530,118	683	NR		NR		NR
1952	683,077	618	NR		NR		NR
1953	449,146	462	NR		NR		NR
1954	682,720	518	NR		NR		NR
1955	555,156	345	NR		NR		NR
1956	611,936	530	NR		NR		NR
1957	486,799	389	NR		NR		NR
1958	763,094	552	NR		NR		NR
1959	406,162	385	NR		NR		NR
1960	441,703	380	NR	42	NR	12	NR
1961	423,919	434	NR	53	NR	14	NR
1962	481,530	408	NR	43	NR	8	NR
1963	385,156	364	NR	48	NR	16	NR
1964	458,083	421	NR	50	NR	53	NR
1965	261,904	276	NR	31	NR	16	NR
1966	204,136	261	NR	43	46,975	12	NR
1967	62,705	81	NR	37	46,888	16	NR
1968	22,231	24	152,209	25	49,371	24	NR
1969	25,826	41	90,918	22	57,686	29	62
1970	47,351	89	104,953	16	56,552	31	67
1971	75,290	90	124,939	22	45,086	20	44
1972	32,275	24	74,215	16	25,507	14	32
1973	26,690	23	69,612	12	27,804	16	30
1974	22,094	20	59,128	6	11,917	15	22
1975	24,374	20	59,647	8	16,652	21	32
1976	41,126	12	38,492	8	12,491	12	22
1977	57,345	15	21,436	5	20,395	17	29
1978	26,871	11	16,817	3	18,269	10	30
1979	13,597	6	14,255	2	11,795	1	57
1980	13,506	11	8,576	2	3,904	1	14
1981	3,124	2	4,941	1	2,077	5	10

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	Measles		Mumps		Rubella		CRS
Year	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases
1982	1,714	2	5,270	2	2,325	4	13
1983	1,497	4	3,355	2	970	3	7
1984	2,587	1	3,021	1	752	1	2
1985	2,822	4	2,982	0	630	1	2
1986	6,282	2	7,790	0	55	1	13
1987	3,655	2	12,848	2	306	0	3
1988	3,396	3	4,866	2	225	1	2
1989	18,193	32	5,712	3	396	4	2
1990	27,786	64	5,292	1	1,125	8	32
1991	9,643	27	4,264	1	1,401	1	34
1992	2,237	4	2,572	0	160	1	11
1993	312	0	1,692	0	192	0	4
1994	963	0	1,537	0	227	0	7
1995	309	2	906	0	128	1	3
1996	508	1	751	1	238	0	2
1997	138	2	683	0	181	0	9
1998	100	0	666	1	364	0	9
1999	100	2	387	1	267	0	6
2000	86	1	338	2	176	0	8
2001	116	1	266	0	23	2	3
2002	44	0	270	1	18	0	1
2003	56	1	231	0	7	0	4
2004	37	NA	258	NA	10	NA	0
2005	66	NA	314	NA	11	NA	1
2006	55	NA	6,584	NA	11	NA	1
2007*	30	NA	715	NA	11	NA	0

	Hepatitis A		Hepatitis B		Haemophilus		Varicella	
Year	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
1966	32,859	NA	1,497	NA	NR	NR	NR	NA
1967	38,909	NA	2,458	NA	NR	NR	NR	NA
1968	45,893	NA	4,829	NA	NR	NR	NR	NA
1969	48,416	NA	5,909	NA	NR	NR	NR	NA
1970	56,797	NA	8,310	NA	NR	NR	NR	NA
1971	59,606	NA	9,556	NA	NR	NR	NR	NA
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

Appendix G

	Hepatitis A		Hepatitis B		Haemophilus		Varicella	
Year	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
1997	30,021	127	10,416	1,030	1,162	7	98,727	99
1998	23,229	114	10,258	1,052	1,194	11	82,455	81
1999	17,047	134	7,694	832	1,309	6	46,016	48
2000	13,397	106	8,036	886	1,398	6	27,382	44
2001	10,609	83	7,843	769	1,597	11	22,536	26
2002	8,795	76	7,996	762	1,743	7	22,841	32
2003	7,653	54	7,526	685	2,013	5	20,948	16
2004	5,970	NA	6,741	NA	2,085	NA	26,659	NA
2005	4,488	NA	5,119	NA	2,304	NA	32,242	NA
2006	3,579	NA	4,713	NA	2,436	NA	48,445	NA
2007*	2,708	NA	3,936	NA	2,231	NA	34,507	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 2006, 29 cases of invasive Hi type B disease were reported among children younger than 5 years of age. Provisional 2007 total for this age group is 17 cases.

Varicella was removed from the nationally notifiable disease list in 1991. In 2006, varicella cases were reported from 28 states, the District of Columbia, Guam, and Puerto Rico.

Sources:
Final totals for 2006: *MMWR* 2007;56(33):851-64.
Final totals for 2005: *MMWR* 2006;55(32):883-93.
Final totals for 2004: MMWR 2004;53(53).
Reportable diseases (1972-2003): Summary of Notifiable Diseases, United States, 2003. *MMWR* 2003;52(54).
Reportable disease (1950-1971): Earlier editions of Summary of Notifiable Diseases, published annually in *MMWR*.

Deaths: National Center for Health Statistics Mortality Report for respective years.

23 January 2008

Impact of Vaccines in the 20th & 21st Centuries

Disease	20th Century Annual Morbidity	2006 Total	% Decrease
Smallpox	48,164	0	100
Diphtheria	175,885	0	100
Pertussis	147,271	15,632	89
Tetanus	1,314	41	97
Polio (paralytic)	16,316	0	100
Measles	503,282	55	>99.9
Mumps	152,209	6,584	96
Rubella	47,745	11	>99.9
Congenital rubella	823	1	99.8
Haemophilus influenzae (<5 years)	20,000 (est)	208 (serotype B or unknown serotype)	99

Sources:

1. CDC. Impact of vaccines universally recommended for children – United States, 1900-1998. *MMWR* 1999;48(12): 243-8

2. CDC. Notice to Readers: Final 2006 Reports of Notifiable Diseases. *MMWR* 2007;56(33):851-64

3/1/08

Appendix G

Vaccine Coverage Levels – United States, 1962-2006

Year	DTP3+	DTP4+	Polio3+	MMR*	Hib3+	Var	PCV3+	HepB3+	Combined 4-3-1	Combined 4-3-1-3
1962	67.3									
1963	71.4									
1964	74.6									
1965	72.7									
1966	74.0									
1967	77.9			60.0						
1968	76.8			61.5						
1969	77.4			61.4						
1970	76.4			58.4						
1971	77.8			62.2						
1972	74.1			62.8						
1973	71.7		59.5	61.0						
1974	72.4		60.0	63.4						
1975	73.2		63.6	65.5						
1976	72.7		61.3	66.3						
1977	69.6		62.6	65.0						
1978	66.6		59.5	63.6						
1979	64.4		59.7	66.5						
1980	66.0		58.9	66.6						
1981	68.1		59.2	66.8						
1982	67.1		57.0	67.6						
1983	65.4		56.9	66.3						
1984	65.0		53.2	65.8						
1985	63.6		53.6	61.2						
1986										
1987										
1988										
1989										

Year	DTP3+	DTP4+	Polio3+	MMR*	Hib3+	Var	PCV3+	HepB3+	Combined 4-3-1	Combined 4-3-1-3
1990										
1991	68.8		53.2	82.0						
1992	83.0	59.0	72.4	82.5	28.2			8.0	68.7	55.3
1993	88.2	72.1	78.9	84.1	55.0			16.3	67.1	
1994	93.0	77.7	83.0	89.0	86.0			37.0	75.0	
1995	94.7	78.5	87.9	87.6	91.7			68.0	76.2	74.2
1996	95.0	81.1	91.1	90.7	91.7	16.0		81.8	78.4	76.5
1997	95.5	81.5	90.8	90.5	92.7	25.9		83.7	77.9	76.2
1998	95.6	83.9	90.8	92.0	93.4	43.2		87.0	80.6	79.2
1999	95.9	83.3	89.6	91.5	93.5	57.5		88.1	79.9	78.4
2000	94.1	81.7	89.5	90.5	93.4	67.8		90.3	77.6	76.2
2001	94.3	82.1	89.4	91.4	93.0	76.3		88.9	78.6	77.2
2002	94.9	81.6	90.2	91.6	93.1	80.6	40.8	89.9	78.5	77.5
2003	96.0	84.8	91.6	93.0	93.9	84.8	68.1	92.4	82.2	81.3
2004	95.9	85.5	91.6	93.0	93.5	87.5	73.2	92.4	83.5	82.5
2005	96.1	85.7	91.7	91.5	93.9	87.9	82.8	92.9	83.1	82.4
2006	95.8	85.2	92.9	92.4	93.4	89.3	87.0	93.4	83.2	82.3

*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 Local Area Vaccination Coverage Among Children Aged 19-35 Months – United States, 2006. *MMWR* 2007;56(34);880-885.

Appendix G

APPENDIX H

Standards

Standards for Child and Adolescent Immunization Practices H-1

Standards for Adult Immunization Practices H-21

Essential Public Health Services. H-40

Adult Immunization: Summary of the National Vaccine Advisory Committee Report, *JAMA* **1994;272:1133-7. . . . . H-42**

Appendix H

Standards for Child and Adolescent Immunization Practices

Copies may be requested from:

Centers for Disease Control and Prevention
National Center for Immunization and Respiratory Diseases
Resource Center
1600 Clifton Road
Mailstop E-34
Atlanta, GA 30333-0418

Appendix H

Introduction H-3

Standards. H-5

References. H-14

Endorsements H-15

National Vaccine Advisory Committee (NVAC). H-17

Acknowledgements. H-19

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/vaccines/programs/vfc/default.htm

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/vaccines/recs/vac-admin/contraindications.htm*), 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 Immunization Program Managers

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Standards for Adult Immunization Practices

Copies may be requested from:

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National Center for Immunization and Respiratory Diseases
Resource Center
1600 Clifton Road
Mailstop E-34
Atlanta, GA 30333-0418

The Standards for Adult Immunization Practices
are also published in
the *American Journal of Preventive Medicine* 2003;25(2)

Appendix H

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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).

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).

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

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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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-preventable 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.[21]

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 1980s 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 95% 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 or 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.[23] 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.[25]

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.[18,34] 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,[35] a new strain of *Vibrio cholerae* in South Asia,[36] and the spread of antimicrobial-resistant *Streptococcus pneumoniae* in many countries.[37] 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 microbiologi-

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 15 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:

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APPENDIX I

Immunization Resources

National Immunization Program Contact Information I-1

IAC Online Directory of Immunization Resources I-2

Sample IAC Print Materials I-3

***IAC Express* Information Sheet I-4**

"Immunization Techniques" Video Order Form I-5

Global Vaccination Information Websites I-6

State and Local Immunization Grantee Contact Information I-7

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

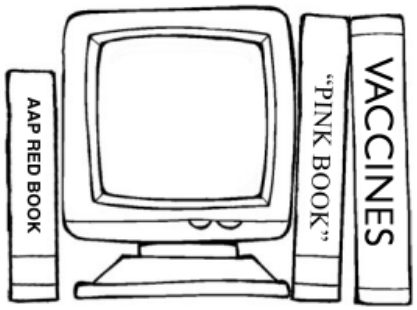
Calendar of upcoming events, online access to publications such as ACIP statements and Vaccine Information Statements, online publications ordering, vaccine safety information, latest pediatric and adult immunization schedules, downloadable Clinic Assessment Software Application (CASA), Frequently Asked 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 News Services:** 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.
- **Government Agencies:** Links to most federal agencies (e.g., CDC, FDA) and state health departments.
- **Videos and more:** Helpful videos, DVDs, and other electronic formats for providers, patients, and parents to learn more about immunization and viral hepatitis.

www.immunize.org/news.d/6012resr.pdf • Item #U6012 (1/06)

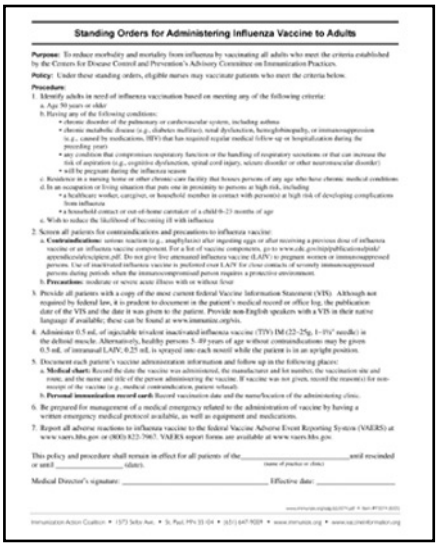
Immunization Action Coalition • 1573 Selby Ave. • St. Paul, MN 55104 • (651) 647-9009 • www.immunize.org • www.vaccineinformation.org

Sample IAC Print Materials

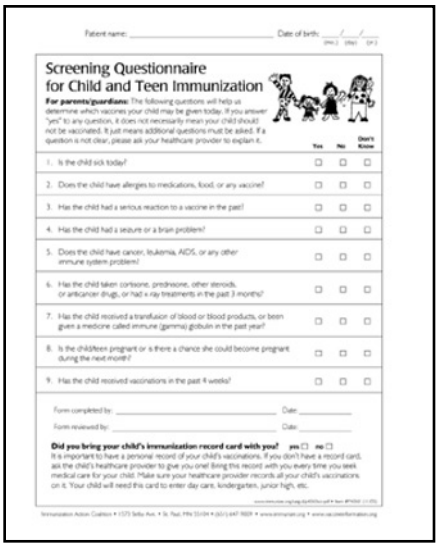
These, and many other useful materials for both providers and patients, can be downloaded free of charge from the IAC's website at http://www.immunize.org/catg.d/free.htm


Vaccine Administration Record for Children and Teens

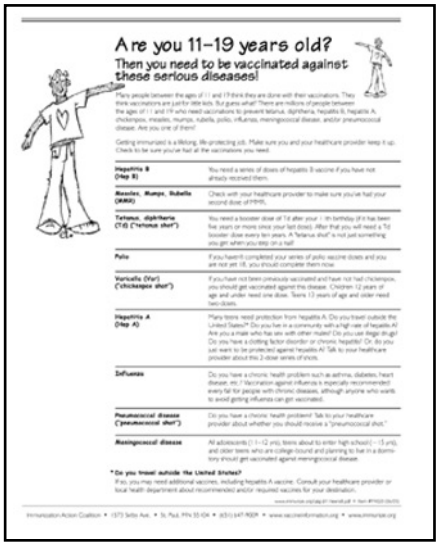
Vaccine AdministrationRecord
for Children and Teens
http://www.immunize.org/catg.d/p2022b.pdf


Standing Orders for Administering Influenza Vaccine to Adults

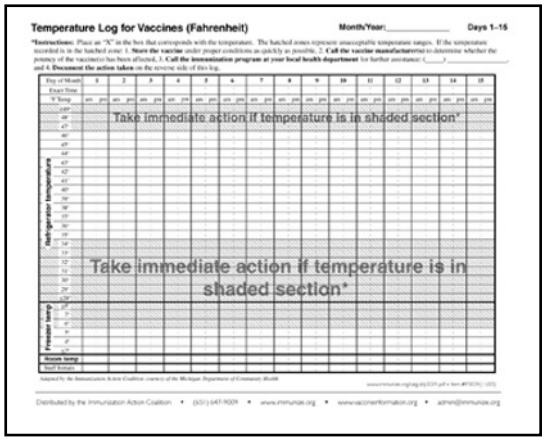
Standing Orders for Administering
Influenza Vaccine to Adults
http://www.immunize.org/catg.d/p3074.pdf


Screening Questionnaire for Child and Teen Immunization

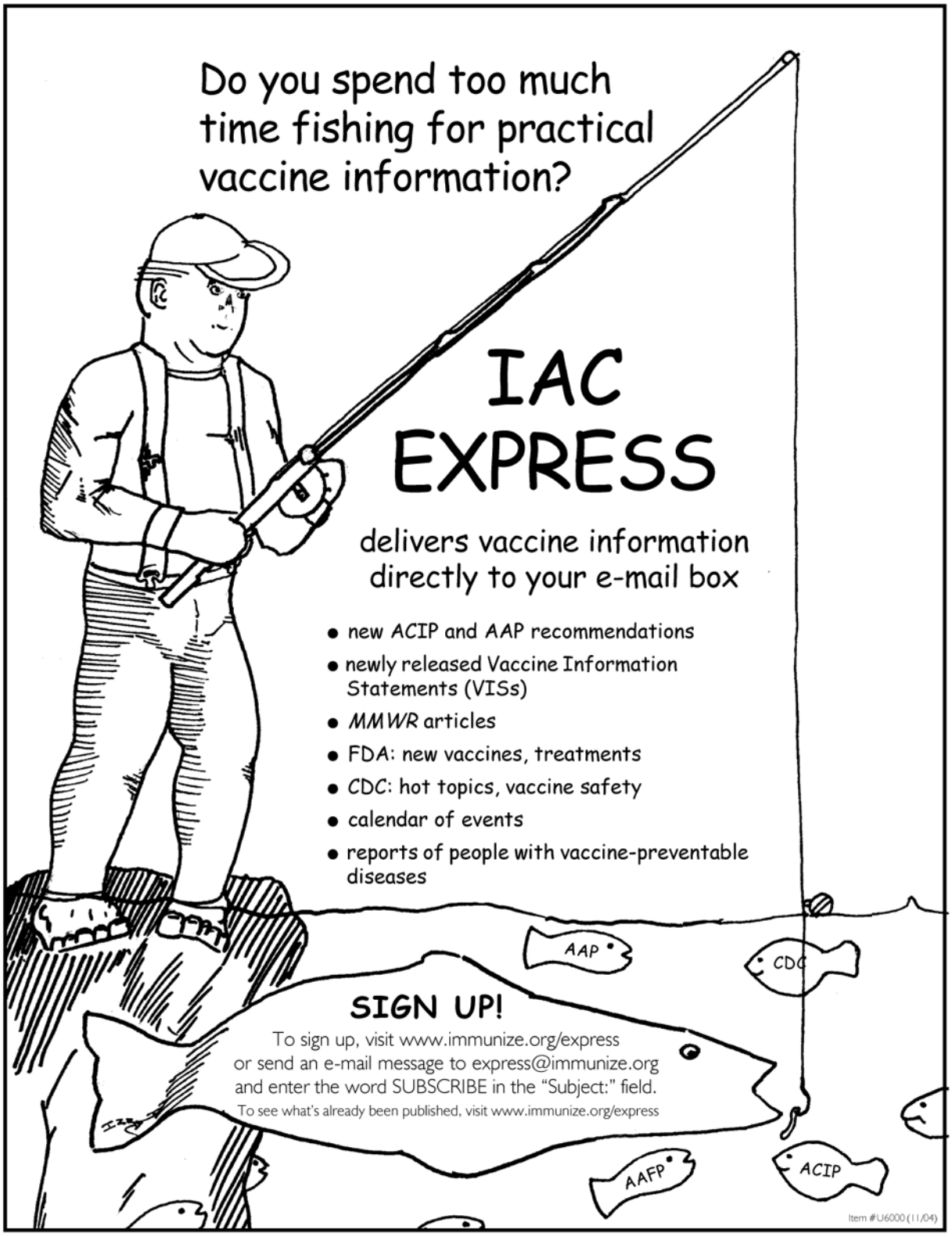
Screening Questionnaire
for Child and Teen Immunization
http://www.immunize.org/catg.d/p4060scr.pdf


Are You 11-19 Years Old?

Are You 11-19 Years Old?
http://www.immunize.org/catg.d/11teens8.pdf


Temperature Log for Vaccines (Fahrenheit)

Temperature Log for Vaccines (Fahrenheit)
http://www.immunize.org/catg.d/p3039pdf



Immunization Action Coalition • 1573 Selby Avenue • St. Paul, MN 55104 • (651) 647-9009 • www.immunize.org



IMMUNIZATION TECHNIQUES

Safe • Effective • Caring

Order Form

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.

Billing Information

Please print clearly and minimize use of abbreviations

Name:_____

Organization:_____ Dept:_____

Address:_____

City:_____ State:_____ Zip:_____

Telephone: (_____)_____ E-mail:_____

Shipping Information (If different from Billing Information)

Name:_____

Organization:_____ Dept:_____

Address:_____

City:_____ State:_____ Zip:_____

Telephone: (_____)_____ E-mail:_____

Item #	Item Name	Quantity	Unit Price	Total
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	
			Balance Due	

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	

Make checks or money orders payable to: **California Distance Learning Health Network**

We also accept purchase order numbers. PO#_____

Credit Card Information

Credit card type: ☐ Visa ☐ MasterCard

Credit card number: _____

Expiration date: _____/_____ (mo.) (yr.)

Signature of card holder: _____

Fax your order to (619) 594-2111 or order online at www.cdlhn.com.

For inquiries contact:

California Distance Learning Health Network

9245 Sky Park Court, Suite 100, San Diego, CA 92123 (619) 594-5933 orders@cdlhn.com

www.cdlhn.com

California Distance Learning Health Network is an authorized distributor of the Immunization Techniques suite of products.

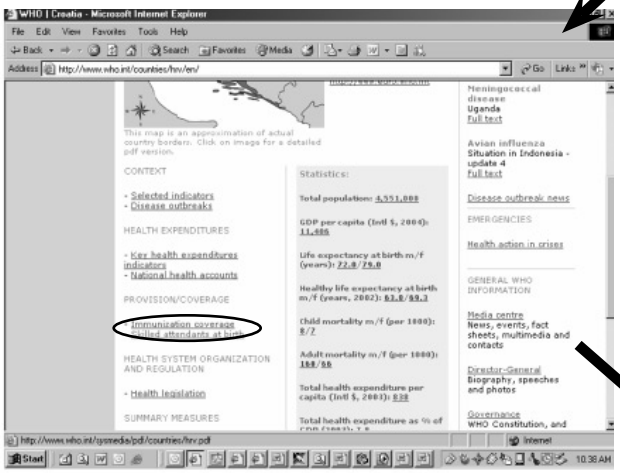
WHO Global Vaccination Information



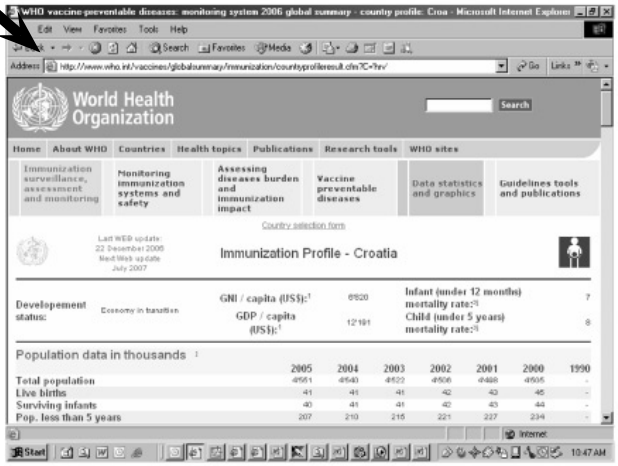
Go to the World Health Organization webpage: **http://www.who.int/countries/en/**



Select a country to access maps, statistics and other health-related information about that country



Click on “Immunization coverage” (in the left column) to access a national **Immunization Profile** for the country, which includes information on population, disease incidence, vaccine coverage, and the routine vaccination schedule.



NATIONAL IMMUNIZATION PROGRAM
IMMUNIZATION GRANTEES
December 18, 2006

(see **http://www2a.cdc.gov/nip/progmgr/fieldstaff.asp?rpt=pm** for updated list)

STATE & CITY GRANTEES

ALABAMA
Alabama Department of Public Health
State Immunization Program
P.O. Box 303017
Montgomery, AL 36130-3017

PHONE #: (334) 206-5023
FAX #: (334) 206-2044
Program Manager: Winkler Sims
Email: wsims@adph.state.al.us

Fed Ex: Disease Control/Immunization Div.
The RSA Tower
201 Monroe St., Suite 1460
Montgomery, AL 36104

ALASKA
Alaska Department of Health and Social Services
Immunization Program
3601 C. Street, Suite 540
P.O. Box 240249
Anchorage, Alaska 99503

PHONE #: (907) 269-8000
FAX #: (907) 562-7802
Program Manager: 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: Charles.Beets@Arkansas.gov

CALIFORNIA
California Department of Health Svcs
Immunization Branch
850 Marina Bay Parkway, Building P
Richmond, California 94804-6403

PHONE #: (510) 540-2065
FAX #: (510) 883-6015
Program Manager: 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: Joni Reynolds
Email: Joni.Reynolds@state.co.us

CONNECTICUT
Connecticut State Dept of Public Health
Immunization Program
P.O. Box 340308
410 Capitol Avenue, MS# 11 MUN
Hartford, Connecticut 06134-0308

PHONE #: (860) 509-7929
FAX #: (860) 509-7945
ProgramManager: Vincent Sacco
Email: vincent.sacco@po.state.ct.us

DELAWARE
Immunization Program/Div of Public Health
Delaware Dept of Health & Social Services
Blue Hen Corporate Center
655 South Bay Rd, Suite 218, Room 111
Dover, Delaware 19901

PHONE #: (302) 741-2940
FAX #: (302) 739-2358
ProgramManager: 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., Suite 13-476
Atlanta, Georgia 30303

PHONE #: (404) 657-3158
FAX #: (404) 657-1463
Program Manager: Michelle Conner
Email: mmconner@dhr.state.ga.us

HAWAII
Hawaii Department of Health
Immunization Program
1250 Punchbowl Street - Room 428
P.O. Box 3378
Honolulu, Hawaii 96801
Fed Ex: 1250 Punchbowl St., Rm 428
Honolulu, Hawaii 96813

PHONE #: (808) 586-8300
FAX #: (808) 586-8302
Program Manager: Kathleen Fazekas
Email: kathie.fazekas@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.gov

IOWA
Iowa Department of Public Health
Division of Family/Community Health
321 E. 12th Street
Des Moines, Iowa 50319-0075
PHONE #: (515) 281-4923
FAX #: (800) 831-6292
Program Manager: Don Callaghan
Email: dcallagh@idph.state.ia.us

KANSAS
Kansas State Department of Health
Bureau of Disease Prevention
900 S.W. Jackson Street
L.S.O.B Suite 901 N
Topeka, Kansas 66612-1274
PHONE #: (785) 296-5591
FAX #: (785) 296-6368
Program Manager: 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: Dave.Miller@ky.gov

LOUISIANA
Louisiana Office of Public Health
Immunization Program - Suite 107
1450 L and A Road
Metairie, Louisiana 70001
PHONE #: (504) 838-5300
FAX #: (504) 483-1909
Program Manager: Ruben Tapia
Email: 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: Marie O'Donnell
Email: marie.o'donnell@state.ma.us

MICHIGAN
Michigan Department of Community Health
Division of Immunization
201 Townsend Street
P.O. Box 30195
Lansing, Michigan 48909
PHONE #: (517) 335-8159
FAX #: (517) 335-9855
Program Manager: Bob Swanson
Email: SwansonR@michigan.gov

MINNESOTA
Minnesota Department of Health
Immunization Program
625 N. Roberts Street
P.O. Box 64975
St. Paul, Minnesota 55164-0975
PHONE #: (612) 676-5100
FAX #: (612) 676-5689
Program Manager: Margo Roddy
Email: Margaret.Roddy@health.state.mn.us

MISSISSIPPI
Mississippi State Department of Health
Division of Immunization
570 Woodrow Wilson Blvd
P.O. Box 1700
Jackson, Mississippi 39215-1700

PHONE #: (601) 576-7751
FAX #: (601) 576-7686
Program Manager: Regina Irvin
Email: rirvin@msdh.state.ms.us

MISSOURI
Missouri Department of Health
Section of Vaccine-Preventable Diseases
930 Wildwood Drive
P.O. Box 570
Jefferson City, Missouri 65102

PHONE #: (573) 751-6439
FAX #: (573) 526-6892
Program Manager: Jeannie Ruth
Email: jeannie.ruth@dhss.mo.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@mt.us

NEBRASKA
Nebraska Department of Health & Human Services
Immunization Program
301 Centennial Mall South
P.O. Box 95007
Lincoln, Nebraska 68509-5007

PHONE #: (402) 471-6423
FAX #: (402) 471-6426
Program Manager: Barbara Ludwig
Email: barbara.ludwig@hhss.ne.gov

NEVADA
Nevada State Health Division
Immunization Program
505 King Street, Room 103
Carson City, Nevada 89701

PHONE #: (775) 684-5900
FAX #: (775) 684-8338
Program Manager: Doug Banghart
Email: Dbanghart@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: Angela Sorrells
Email: Angela.Sorrells@doh.state.nj.us

NEW MEXICO
New Mexico Department of Health
Immunization Program
1190 St. Francis Drive
Rennels Building - Suite 1261
Santa Fe, New Mexico 87502

PHONE #: (505) 827-2369
FAX #: (505) 827-2898
Program Manager: Anne Lutz
Email: anne.lutz@state.nm.us

NEW YORK
New York State Department of Health
Immunization Program
Corning Tower Building
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