IMMUNOLOGY AND VACCINE-PREVENTABLE DISEASE

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

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 a few weeks or months.

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

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 in a natural infection with a virus or bacteria, 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 pro-

Principles of Vaccination

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

Principles of Vaccination

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

Passive Immunity
- Protection transferred from another person or animal as antibody

Principles of Vaccination

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

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

tection 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.

Passive Immunity

- Transfer of antibody from an exogenous source
- Transplacental most important source in infancy
- Temporary protection

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 antibody "profile" 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).

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

Sources of Passive Immunity

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

Besides 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 (immune globulin), homologous human hyperimmune globulin, and heterologous hyperimmune serum (antitoxin).

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 U.S. Because it comes from many different donors, it contains antibody to many different antigens. It is used primarily for postexposure prophylaxis for hepatitis A and measles.

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

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

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, autoimmune conditions, and infectious diseases

Immune globulin from human sources is polyclonal - it contains many different kinds of antibodies. In the 1970s, techniques were developed to isolate and "immortalize" (cause to grow indefinitely) single B cells, which led to the development of monoclonal antibody products. Monoclonal antibody is produced from a single clone of B cell, so these products contain antibody to only one antigen or closely related group of antigens. Monoclonal antibody products have many applications, including the diagnosis of certain

types of cancer (colorectal, prostate, ovarian, breast), treatment of cancer (B-cell chronic lymphocytic leukemia, non-Hodgkins lymphoma), prevention of transplant rejection, and treatment of autoimmune diseases (Crohns disease, rheumatoid arthritis) and infectious disease.

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

Antibody for Prevention of RSV

- RSV-IGIV
  - –Human hyperimmune globulin
  - –Contains other antibodies
- Palivizumab (Synagis)
  - –Monoclonal
  - –Contains only RSV antibody

ACTIVE IMMUNITY

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

One way to acquire active immunity is to have the natural disease. In general, once persons recover from infectious diseases, they will be immune to those diseases for the rest of their lives. 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.

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 do not subject the recipient to the disease and its potential complications. Vaccines produce immunologic memory similar to that acquired by having the natural disease.

Vaccination

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

Many factors may influence the immune response to vaccination. These include the presence of maternal antibody, nature and dose of antigen, route of administration, and the presence of adjuvants (*e.g.*, aluminum-containing materials added to improve the immunogenicity of the vaccine). Host factors such as age, nutritional factors, genetics, and coexisting disease, may also affect the response.

CLASSIFICATION OF VACCINES

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

Classification of Vaccines

- Live attenuated
  - –viral
  - –bacterial
- Inactivated

Live attenuated vaccines are produced by modifying a disease-

producing ("wild") virus or bacteria in a laboratory. The resulting vaccine organism retains the ability to replicate (grow) and produce immunity, but usually does not cause illness. Live attenuated vaccines available in the U.S. include live viruses and live bacteria.

Inactivated Vaccines

Whole
- virus
- bacteria

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

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

General Rule

The more similar a vaccine is to the natural disease, the better the immune response to the vaccine.

LIVE ATTENUATED VACCINES

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

Live Attenuated Vaccines

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

In order to produce an immune response, live attenuated vaccines must replicate (grow) in the vaccinated person. A relatively small dose of virus or bacteria is given, which replicates in the body and creates enough virus 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 natural ("wild") organism. When a live attenuated vaccine does cause "disease," it is usually much milder than the natural disease, and is referred to as an adverse reaction.

The immune response to a live attenuated vaccine is virtually identical to that produced by a natural infection. The immune system does not differentiate between an infection with a weakened vaccine virus and an infection with a wild virus. Live attenuated vaccines are generally effective with one dose, except those administered orally.

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

A live attenuated vaccine virus could theoretically revert back 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 due to interference from circulating antibody to the vaccine virus. **Antibody from any source (*e.g.,* transplacental, transfusion) can interfere with growth of the vaccine organism and lead to a 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 labile, and can be damaged or destroyed by heat and light. They must be handled and stored carefully.

Currently available live attenuated viral vaccines include measles, mumps, rubella, vaccinia, varicella, yellow fever, and influenza (intranasal). Oral polio vaccine is a live viral vaccine but is no longer available in the United States. Live recombinant rotavirus vaccine is still licensed in the U.S. but is no longer distributed because of its association with intussusception. Live attenuated bacterial vaccines include BCG and oral typhoid vaccine.

INACTIVATED VACCINES

These vaccines are produced by growing the bacteria 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. Unlike live antigens, inactivated antigens are usually not affected by circulating antibody. Inactivated vaccines may be given when antibody is present in the blood (*e.g.,* in infancy, or following receipt of antibody-containing blood products). Inactivated vaccines always require multiple doses. In general, the first dose does not produce protective immunity, but only "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 fall diminish with time. As a result, some inactivated vaccines may require periodic supplemental doses to increase, or "boost,"

Live Attenuated Vaccines

- Severe reactions possible
- Interference from circulating antibody
- Unstable

Live Attenuated Vaccines

- Viral — measles, mumps, rubella, vaccinia, varicella, yellow fever, influenza, (oral polio) (rotavirus)
- Bacterial — BCG, oral typhoid

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

Inactivated Vaccines

- Cannot replicate
- Minimal interference from circulating antibody
- Generally not as effective as live vaccines
- Generally require 3-5 doses
- Immune response mostly humoral
- Antibody titer diminishes with time

Inactivated Vaccines

Whole cell vaccines
- **Viral** — polio, hepatitis A, rabies (influenza)
- **Bacterial** — (pertussis) (typhoid) (cholera) (plague)

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

Inactivated Vaccines

Fractional vaccines
- **Subunit** — hepatitis B, influenza, acellular pertussis, (Lyme)
- **Toxoid** — diphtheria, tetanus

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

Polysaccharide Vaccines

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

Conjugate polysaccharide
- *Haemophilus influenzae* type b
- pneumococcal

Pure Polysaccharide Vaccines

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

antibody titers.

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

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 is no longer available in the U.S.

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 <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." Repeat doses of polysaccharide vaccines do not cause a booster response. This is not seen with polysaccharide antigens. 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**. 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 *Haemophilus influenzae* type b (Hib). A conjugate vaccine for pneumococcal disease was licensed in 2000. A meningococcal conjugate vaccine may be available in the future.

RECOMBINANT VACCINES

Vaccine antigens may also be produced by genetic engineering technology. These products are sometimes referred to as **recombinant** vaccines. Three genetically-engineered vaccines are currently available in the United States. Hepatitis B vaccines are pro-

duced by insertion of a segment of the hepatitis B virus gene into the gene of a yeast cell. The modified yeast cell produces pure hepatitis B surface antigen when it grows. Live typhoid vaccine (Ty21a) is *Salmonella typhi* bacteria that has been genetically modified to not cause illness. Live attenuated influenza vaccine (LAIV) has been engineered to replicate effectively in the mucosa of the nasopharynx but not in the lungs.

SELECTED REFERENCES

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

The *General Recommendations on Immunization* is a document that addresses issues common to more than one vaccine. It is revised by the Advisory Committee on Immunization Practice every 3-5 years as needed. The most current revision was published in February 2002 (*MMWR* 2002;51(RR-2):1-36). All providers who administer vaccine should have a copy of this document and be familiar with its contents. It can be downloaded from the *MMWR* website or ordered in print version from the National Immunization Program. This chapter discusses issues that are commonly encountered in vaccination practices.

TIMING AND SPACING OF VACCINES

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

Issues Regarding Spacing and Timing of Vaccines

- Interval between receipt of antibody-containing blood products and measles vaccine
- Interval between doses of different vaccines not administered simultaneously
- 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 not substantially affected by circulating antibody, so they can be administered before, after, or at the same time as the antibody. Simultaneous administration of antibody (in the form of immune globulin) and vaccine is recommended for postexposure prophylaxis of certain diseases, such as hepatitis B, rabies, and tetanus.

All live vaccines must replicate in order to cause an immune response. Antibody against parenteral (injected) live vaccine antigen may interfere with replication. If a live parenteral vaccine (MMR or varicella) must be given around the time that antibody is given, the two must be separated by enough time so that the antibody does not interfere with viral replication. If the live vaccine is given first, it is necessary to wait **at least 2 weeks** *(i.e.*, an incubation period) before giving the antibody. If the interval between the

Antibody and Live Vaccines

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

vaccine and antibody is less than 2 weeks, the recipient should be tested for immunity or the vaccine dose should be repeated.

If the antibody is given before a dose of MMR or varicella vaccine, it is necessary to wait until the antibody has waned (degraded) before giving the vaccine to reduce the chance of interference by the antibody. The necessary interval between an antibody-containing product and MMR or varicella vaccine depends on the concentration of antibody in the product. A table listing the recommended intervals between antibody products and live vaccines (MMR and varicella) is included in Appendix A, and in the *General Recommendations on Immunization*. The interval between administration of an antibody product and MMR or varicella vaccination can be as long as 11 months.

Although passively acquired antibodies can interfere with the response to rubella vaccine, the low dose of anti-Rho(D) globulin administered to postpartum women has not been demonstrated to reduce the response to the RA27/3 strain rubella vaccine. Because of the importance of rubella immunity among childbearing age women, the postpartum vaccination of rubella-susceptible women with rubella or MMR vaccine should not be delayed because of receipt of anti-Rho(D) globulin or any other blood product during the last trimester of pregnancy or at delivery. These women should be vaccinated immediately after delivery and, if possible, tested ≥3 months later to ensure immunity to rubella and, if necessary, to measles.

Antibody for Prevention of RSV

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

Oral typhoid, and yellow fever vaccines are not affected by the administration of immune globulin or blood products. They may be given simultaneously with blood products, or separated by any interval. These vaccines are not affected because few North Americans are immune to yellow fever or typhoid. Consequently, donated blood products in the United States do not contain a significant amount of antibody to these organisms. The effect of circulating antibody on live attenuated influenza vaccine is not known.

Palivizumab (Synagis) contains only monoclonal antibody to respiratory synctial virus (RSV). It does not interfere with the response to live virus vaccines.

SIMULTANEOUS AND NON-SIMULTANEOUS ADMINISTRATION

General Rule

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

The simultaneous administration 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 can be very important in childhood vaccination programs because it increases the probability that a child will be fully immunized at the appropriate age. A study during a recent measles outbreak showed that about one-third of measles cases in unvaccinated but vaccine-eligible preschool children could have been prevented if MMR had been administered at the same visit when another vaccine was given.

Individual vaccines should not be mixed in the same syringe unless they are licensed for mixing by the FDA. Only the Aventis-Pasteur Hib/DTaP (TriHIBit™) vaccine is licensed for mixing in the same syringe.

NONSIMULTANEOUS ADMINISTRATION OF DIFFERENT VACCINES

In some situations, vaccines that could be given simultaneously are not (*e.g.*, if the child is receiving vaccines from two different providers).

Spacing of vaccine combinations not given simultaneously

Combination	Minimum Interval
Two live parenteral	4 weeks
All other	None

Live parenteral (injected) vaccines (MMR, varicella, and yellow fever) that are not administered simultaneously should be separated by at least 4 weeks. This precaution is intended to reduce or eliminate interference from the vaccine given first on the vaccine given later. If two live injected vaccines are not administered simultaneously but are separated by less than 4 weeks, the vaccine given second should be repeated in ≥ 4 weeks or confirmed to be effective by serologic testing of the recipient. An exception to this recommendation is yellow fever vaccine administered <4 weeks after single antigen measles vaccine. A 1999 study demonstrated that yellow fever vaccine is not affected by measles vaccine given 1-27 days earlier. The effect of nonsimultaneously administered rubella, mumps, varicella, and yellow fever vaccines is not known.

Spacing of live vaccines not given simultaneously

- If two live parenteral vaccines are given <4 weeks days apart the vaccine given second should be repeated.
- Exception is yellow fever vaccine given <4 weeks after measles vaccine.

Live vaccines administered by a nonparenteral route (OPV, oral typhoid, live attenuated influenza) are not believed to interfere with each other if not given simultaneously. These vaccines may be given at any time before or after each other. Oral typhoid is not licensed for children less than 6 years of age, and OPV is no longer available in the United States, so these vaccines are not likely to be given to the same child.

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

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.

Minimum Intervals and Ages

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

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

Administering doses of a multidose vaccine at shorter than the recommended intervals might be necessary in circumstances where 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 less than 12 months (this dose would not be counted, and would be repeated at >12 months of age). The second consideration involves administering a dose a few days earlier than the minimum interval or age, which is unlikely to have a substantially negative effect on the immune response to that dose. Although **vaccinations should not be scheduled at an interval or age less than the recommended minimums,** a child may have erroneously been brought to the office early, or may have come for an appointment not specifically for vaccination (for example, for an ear recheck). In this situation, the clinician can consider administering the vaccine earlier than the minimum interval or age. If the parent/child is known to the clinician and is reliable, it is preferable to reschedule the child for vaccination closer to the recommended interval. If the parent/child is not known to the clinician or is not reliable (*e.g.*, habitually misses appoint-

ments), it is preferable to administer the vaccine at that visit than to reschedule the child for a later visit which may not be kept.

Vaccine doses administered up to four days before the minimum interval or age can be counted as valid. This four day recommendation does not apply to rabies vaccine because of the unique schedule for this vaccine. Doses administered five days or earlier than the minimum interval or age should not be counted as valid doses and should be repeated as age appropriate. The repeat dose should be spaced after the invalid dose by a time greater than the recommended minimum interval shown in Table 1 of the General Recommendations. In certain situations, local or state requirements might mandate that doses of selected vaccines be administered on or after specific ages, precluding these four-day recommendations.

Violation of Minimum Intervals or Minimum Age

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

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 was completed. Consequently, **it is not necessary to restart the series or add doses of any vaccine due to an extended interval between doses.** The only exception to this rule is oral typhoid vaccine in some circumstances. In the case of oral typhoid, some experts recommend repeating the series if the 4 dose series is extended to more than 3 weeks.

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

NUMBER OF DOSES

General Rule

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

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

For live injected vaccines, the first dose usually provides protection. An additional dose is given to ensure seroconversion. For instance, 95% to 98% of recipients will respond to a single dose of measles vaccine. The second dose is given to assure 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 usually does not provide protection. 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, 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

Vaccine Adverse Reaction

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

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

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.

Vaccine Adverse Reactions

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

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 in up to 50 percent of vaccine doses, depending on the type of vaccine. Local reactions are most common with inactivated vaccines, particularly those, such as DTaP, that contain adjuvants. Local adverse reactions generally occur within a few hours of the injection and are usually mild and self-limited. On rare occasions, local reactions may be very exagerated or severe. These are often referred to as hypersensitivity reactions, although they are not allergic, as the term implies. These reactions are also known as Arthus reactions, and are most commonly seen with tetanus and diphtheria toxoids. Arthus reactions are believed to be due to very high titers of antibody, usually because of too many doses of toxoid.

Vaccine Adverse Reactions

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

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, and may occur in a vaccinated persons because of the vaccine, or may be caused by something unrelated to the vaccine, like a concomitant viral infection.

Systemic adverse reactions were relatively frequent with whole cell DTP vaccine. However, comparison of the frequency of systemic adverse events among vaccine and placebo recipients show they are uncommon with inactivated vaccines currently in use, including acellular pertussis vaccine.

Systemic adverse reactions may occur following live attenuated vaccines. Live attenuated vaccines must replicate in order to produce immunity. The adverse reactions that follow live attenuated vaccines,

such as fever or rash represent symptoms produced from that replication, and are similar to a mild form of the natural disease. Systemic adverse reactions following live vaccines are usually mild, and occur a week or two after the vaccine was given (*i.e.*, after an incubation period of the vaccine virus). Live attenuated influenza virus 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.

Live Attenuated Vaccines

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

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

Vaccine Adverse Reactions

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

REPORTING VACCINE ADVERSE EVENTS

From 1978 to 1990, the CDC conducted the Monitoring System for Adverse Events Following Immunization (MSAEFI) in the public sector. In 1990, MSAEFI was replaced by the Vaccine Adverse Events Reporting System (VAERS), which includes reporting from both public and private sectors. Providers should report any clinically significant adverse event that occurs after the administration of any vaccine licensed in the United States. Providers should report 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 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://www.vaers.org. VAERS now accepts reports of adverse reactions through their online system.

CONTRAINDICATIONS AND PRECAUTIONS TO VACCINATION

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

Contraindication

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

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 illnes or death in the recipient. In gen-

Precaution

- A condition in a recipient which may increase the chance or severity of an adverse reaction, or
- May 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 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

eral, 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 which *may increase* the chance or severity of a serious adverse reaction, or that may compromise the ability of the vaccine to produce immunity (such as administering measles vaccine to a person with passive immunity to measles from a blood transfusion). Injury could result, but the chance of this happening is less than with a contraindication. In general, vaccines are deferred when a precaution condition is present. However, situations may arise when the benefit of protection from the vaccine outweighs the risk of an adverse reaction, and a provider may decide to give the vaccine. For example, prolonged crying or a high fever after a dose of whole cell or acellular pertussis vaccine is considered a precaution to subsequent doses of pertussis vaccine. But if the child were at high risk of pertussis exposure (*e.g.*, 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) allergy to a vaccine component or following a prior dose of a vaccine**, and **encephalopathy within 7 days of pertussis vaccination**.

Four conditions are considered permanent precautions to further doses of pertussis-containing vaccine: temperature >105°F, collapse or shock-like state (hypotonic hyporesponsive episode), and 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.

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

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 which are mediated by IgE, occur within minutes or hours of the vaccine, and require medical attention. Examples of severe allergic reactions are generalized urticaria (hives), swelling of the mouth and throat, difficulty breathing, wheezing, hypotension, or shock. With appropriate screening these reactions are very rare following vaccination. A table listing vaccine contents is included in Appendix A.

Persons may be allergic to the vaccine antigen, animal protein, antibiotics, preservatives, or stabilizers. The most common animal

protein allergen is egg protein found in vaccines prepared using embryonated chicken eggs (*e.g.*, yellow fever and influenza vaccines). **Ordinarily, persons who are able to eat eggs or egg products can receive vaccines that contain egg**; persons with histories of anaphylactic or anaphylactic-like allergy to eggs or egg proteins should not. Asking persons whether they can eat eggs without adverse effects is a reasonable way to screen for those who might be at risk from receiving yellow fever, and influenza vaccines.

Several 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 it may be gelatin, not egg, that causes allergic reactions to MMR. As a result, in 1998, 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 anaphylactic reactions to neomycin should not receive these vaccines. Most often, neomycin allergy is a contact dermatitis, a manifestation of a delayed type (cell-mediated) immune response, rather than anaphylaxis. A history of delayed type reactions to neomycin is not a contraindication for administration of these vaccines.

Latex is liquid sap from the commercial rubber tree. Latex contains naturally occurring impurities (*e.g.*, plant proteins and peptides), which are believed to be responsible for allergic reactions. Latex is processed to form natural rubber latex and dry natural rubber. Dry natural rubber and natural rubber latex might contain the same plant impurities as latex but in a lesser amounts. Natural rubber latex is used to produce medical gloves, catheters, and other products. Dry natural rubber is used in syringe plungers, vial stoppers, and injection ports on intravascular tubing. Synthetic rubber and synthetic latex also are used in medical gloves, syringe plungers, and vial stoppers. Synthetic rubber and synthetic latex do not contain natural rubber or natural latex, and therefore, do not contain the impurities linked to allergic reactions.

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

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

latex gloves), vaccines supplied in vials or syringes that contain dry natural rubber or natural rubber latex can be administered.

PREGNANCY

The concern about vaccinating pregnant women is with infection of the fetus, and is theoretical. There is no evidence that any live vaccine (including rubella) causes birth defects. See the rubella chapter for more information. However, since the theoretical possibility exists, live vaccines should not be given to women known to be pregnant.

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

IMMUNOSUPPRESSION

Immunosuppression

Disease

- Congenital immunodeficiency
- Leukemia or lymphoma
- Generalized malignancy

Live vaccines can cause severe or fatal reactions in immunosuppressed persons due to uncontrolled replication of the vaccine virus, particularly vaccinia and oral polio vaccine virus (and rarely measles and varicella vaccine virus). Severely immunosuppressed persons should not be given live vaccines for this reason. Persons with isolated B-cell deficiency may receive varicella vaccine. Inactivated vaccines cannot replicate, so are safe to use in immunosuppressed persons. However, response to the vaccine may be decreased.

Immunosuppression

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 and varicella vaccines may be given when an immunosuppressed person lives in the same house.

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

Immunosuppression

Corticosteroids

- $\geq$20 mg per day
- $\geq$2 mg/kg per day
- NOT aerosols, topical, alternate day, short courses

Aerosolized steroids, such as inhalers for asthma, alternate day, rapidly tapering, and short (<14 days) high dose schedules, topical formulations, and physiologic replacement schedules are not contraindications to vaccination.

Inactivated vaccines are not contraindicated for immunosuppressed persons. However, response to the vaccine may be poor. A relatively functional immune system is required in order 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* and in a specific Altered Immunocompetence ACIP statement.

HIV INFECTION

Persons infected with human immunodeficiency virus (HIV) may have no symptoms, or may be severely immunosuppressed. In general, the same vaccination recommendations apply as with other types of immunosuppression. Live virus vaccines are usually contraindicated, and inactivated vaccines are not contraindicated.

Measles and varicella can be very severe illnesses in persons with HIV infection and are often associated with complications. Therefore, measles vaccine (as combination MMR vaccine) and varicella vaccine are recommended for persons with HIV infection who are asymptomatic or mildly immunosuppressed. However, persons with severe immunosuppression due to HIV infection should not receive measles vaccine, MMR, or varicella vaccine. Susceptible household contacts of persons with HIV infection should receive MMR and varicella vaccines. Persons with HIV infection should not receive live attenuated influenza vaccine; they should receive inactivated influenza vaccine.

Recommendations for Routine Immunization of HIV-infected Children

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

Yes=vaccinate No=do not vaccinate

VACCINATION OF HEMATOPOIETIC STEM CELL TRANSPLANT RECIPIENTS

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

Antibody titers to vaccine-preventable diseases (*e.g.*, tetanus, poliovirus, measles, mumps, rubella, and encapsulated bacteria) 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, including those caused by encapsulated bacteria (*i.e.*, pneumococcal and Hib infections). As a result, HSCT recipients should be routinely revaccinated after HSCT, regardless of the source of the transplanted stem cells. Revaccination with inactivated vaccines should begin 12 months after HSCT. An exception to this recommendation is for influenza vaccine, which should be administered at ≥6 months after HSCT and annually thereafter for the life of the recipient. MMR vaccine should be be administered 24 months after transplantation if the HSCT recipient is presumed to be immunocompetent. Varicella, meningococcal, and pneumococcal conjugate vaccines are not currently recommended for HSCT recipients because of insufficient experience using these vaccines among HSCT recipients.

Vaccination of Hematopoietic Stem Cell Transplant Recipients

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

Vaccination of Hematopoietic Stem Cell Transplant Recipients

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

Household and other close contacts of HSCT recipients and healthcare workers who care for HSCT recipients, should be appropriately vaccinated, particularly against influenza, measles, and varicella. Additional details of vaccination of HSCT recipients and their contacts can be found in a specific CDC report on this topic.

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.

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

RECENT BLOOD PRODUCTS

Blood products may interfere with the replication of live parenteral (injected) vaccine viruses. Recent receipt of blood products is a precaution to MMR and varicella vaccines. The effect of recent receipt of blood products on live attenuated influenza vaccine is not known. Oral typhoid is not affected by circulating antibody, and blood products in the United States do not contain sufficient yellow fever antibody to interfere with replication of that vaccine. Palivizumab (Synagis) is a monoclonal antibody product used to prevent RSV infection. It contains only antibody to RSV, so will not interfere with live virus vaccination.

Varicella and MMR vaccines should be given 14 days prior to the blood product, or delayed until the antibody has degraded (see table in Appendix A, page A5). If MMR is given sooner than the minimum interval shown, the recipient should be tested for immunity or the dose repeated after the appropriate interval.

Inactivated vaccines are not substantially affected by circulating antibody from blood products and are not contraindicated.

Invalid Contraindications to Vaccination

- Mild illness
- Antibiotic therapy
- Disease exposure or convalescence
- Pregnancy in the household
- Breastfeeding
- Premature birth
- Allergies to products not in vaccine
- Family history unrelated to immunosuppression
- Need for TB skin testing
- Need for multiple vaccines

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, and result in missed opportunities to administer needed vaccines. Some of the most common invalid contraindications are minor illnesses, conditions related to pregnancy and breastfeeding, allergies that are not anaphylactic in nature, and certain aspects of the patient's family history.

MINOR ILLNESS

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

Several large studies have shown that young children with URI, otitis media, diarrhea, and/or fever respond to measles vaccine as well as those without these conditions. These large studies refute the results of an earlier small study (Krober, *JAMA* 1991) which suggested that minor infections such as URIs might impair the response to measles vaccine. Further, there is no evidence that mild diarrhea reduces the success of immunization of infants in this country.

Low grade fever is not a contraindication to immunization. Temperature measurement is not necessary before immunization if the infant or child does not appear ill and the parent does not say the child is currently ill.

Invalid Contraindications
Minor Illness

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

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

ANTIBIOTIC THERAPY

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

DISEASE EXPOSURE OR CONVALESCENCE

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

PREGNANCY OR IMMUNOSUPPRESSION IN THE HOUSEHOLD OR BREASTFEEDING

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

Most vaccines, including live vaccines (MMR, varicella, and yellow fever) can be given to infants or children with pregnant or immunosuppressed household contacts, as well as to breast-feeding infants. Vaccinia (smallpox) vaccine is not recommended for persons with a pregnant or immunosuppressed household contact in non-emergency situations. Live attenuated influenza vaccine is not recommended for persons who have close contact with an immunosuppressed person, such as a healthcare worker or household contact.

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 breast milk, but transmission to an infant has rarely been documented (rubella is not trans-

mitted by mouth). Transmission of varicella vaccine virus is uncommon, and most women and older immunosuppressed persons are immune from prior chickenpox. Oral polio vaccine virus is shed and can spread, but pregnant contacts are at no greater risk than other household contacts in this situation, and OPV has not been shown to cause fetal defects. Breastfeeding does not decrease the response to routine childhood vaccines. Breastfeeding also does not extend or improve passive immunity to vaccine-preventable disease provided by maternal antibody.

PREMATURE BIRTH

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

Studies demonstrate that decreased seroconversion rates might occur among certain premature infants with low birth weights (*i.e.*, <2,000 grams) after administration of hepatitis B vaccine at birth. However, by one month chronological age, all premature infants, regardless of initial birthweight or gestational age are as likely to respond as adequately as older and larger infants. All premature infants born to hepatitis B surface antigen (HBsAg) positive mothers and mothers with unknown HBsAg status must receive immunoprophylaxis with hepatitis B vaccine and hepatitis B immunoglobulin (HBIG) within 12 hours after birth. If these infants weigh less than 2000 grams at birth, the initial vaccine dose should not be counted towards completion of the hepatitis B vaccine series, and 3 additional doses of hepatitis B vaccine should be administered beginning when the infant is one month of age.

The optimal timing of the first dose of hepatitis B vaccine for premature infants of HBsAg-negative mothers with a birth weight of less than 2000 grams has not been determined. These infants can begin the first dose of the hepatitis B vaccine series at one month of chronological age. Premature infants discharged from the hospital prior to one month chronological age may also be given hepatitis B vaccine at discharge if they are medically stable and showing consistent weight gain.

NONSPECIFIC ALLERGIES, ALLERGIES TO ANTIBIOTICS NOT IN VACCINE, NONSEVERE EGG ALLERGIES, AND ALLERGIES TO DUCK ANTIGENS

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

NONANAPHYLACTIC ALLERGY TO VACCINE COMPONENT

Anaphylactic allergy to a vaccine component (such as egg or neomycin) is a true contraindication to vaccination.
Nonanaphylactic allergy to a vaccine constituent is **not** a contraindication to that vaccine.

FAMILY HISTORY OF ADVERSE REACTIONS UNRELATED TO IMMUNOSUPPRESSION, OR FAMILY HISTORY OF SEIZURES OR SIDS

The only family history that is relevant in the decision to vaccinate a child is immunosuppression, and only for oral poliovirus vaccine. OPV should not be given to a child with a personal or family history of immunosuppression, because the vaccine virus could spread to the immunosuppressed contact.

NEED OR REQUIREMENT FOR TUBERCULOSIS SKIN TEST (PPD)

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

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

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.

How is your child (or how are you) today?
This question screens for concurrent moderate or acute illness. If the child has been examined, this question may not be necessary, or may have already been asked.

Does your child have any allergies to any food or medication?
A severe allergy to a vaccine component is a contraindication to vaccination, so this question must always be asked. It may be more time-efficient to inquire about allergies in a generic way (*i.e.*, any food or medication), rather than to inquire about specific vaccine components. Most parents will not be familiar with minor components of vaccine, but they should know if the child has had an allergic reaction to a food or medication severe enough to require medical attention.

Screening Questions

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

Screening Questions

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

Did the child have any problems after his or her last shots?
This open-ended question explores for allergic reactions to previous doses, and for conditions following pertussis vaccine that may be precautions to additional doses, such as high fever or a hypotonic episode.

Does the child have any problems with his or her immune system?
This question will help identify children with immunodeficiency who generally should not receive live attenuated vaccines, particularly oral polio vaccine.

Does anyone in your household have a problem with their immune system?
Oral polio vaccine and live attenuated influenza vaccine should not be given to a healthy person who has household contact with someone who is immunodeficient.

Has the child received any blood products in the last year, like a transfusion, or immune globulin?
This question helps identify precautions for live attenuated MMR and varicella vaccines, which should not be given to persons who have received passive antibody in the last few months. The question may also expose unreported illnesses that might not have been revealed in earlier questions.

Are you pregnant, or trying to become pregnant?
This question should be asked of **all adolescent and adult women.** MMR and varicella vaccines should not be given to women known to be pregnant or for 4 weeks prior to pregnancy. It is not necessary to inquire about pregnancy in household contacts because a pregnant woman in the household is not a contraindication for administration of any vaccine. ACIP does not recommend pregnancy testing prior to administration of any vaccine.

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

SELECTED REFERENCES

Atkinson W, et al. General Immunization Practices. In: Plotkin SA, OrentseinWA, eds. *Vaccines*. 4th ed., Philadelphia,PA: Saunders, 2003: 91-122.

CDC. General Recommendations on Immunization. Recommendations of the Advisory Committee on Immunization Practices. *MMWR* 2002;51(RR-2):1-36.

CDC. Recommendations of the Advisory Committee on Immunization Practices. Use of vaccines and immune globulins in persons with altered immunocompetence. *MMWR* 1993;42(RR-4):1-18.

CDC. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients: recommendations of the CDC, the Infectious Disease Society of America, and the American Society of Blood and Marrow Transplantation. *MMWR* 2000;49(RR-10):1-128.

American Academy of Pediatrics. Active and Passive Immunization. In: Pickering LK, ed. *Red Book: 2003 Report of the Committee on Infectious Diseases*. 26th ed. Elk Grove Village, IL: American Academy of Pediatrics;2003:1-98.

Dietz VJ, Stevenson J, Zell ER, et al. Potential impact on vaccination coverage levels by administering vaccines simultaneously and reducing dropout rates. *Arch Pediatr Adolesc Med* 1994;148:943-49.

James JM, Burks AW, Roberson RK, Sampson HA. Safe administration of the measles vaccine to children allergic to eggs. *New Eng J Med* 1995;332:1262-69.

King GE, Hadler SC. Simultaneous administration of childhood vaccines: an important public health policy that is safe and efficacious. *Pediatr Infect Dis J* 1994;13:394-407.

Plotkin SA. Vaccines, Vaccination and Vaccinology. *J. Infect Dis* 2003;187:1349-59.

THE NEED TO FOCUS ON STRATEGIES TO INCREASE IMMUNIZATION LEVELS

Vaccine-preventable disease rates are at their lowest level ever. In 2002 there were U.S. reports of only 44 cases of measles, 18 cases of rubella, 1 case of diphtheria, 25 cases of tetanus, and no wild polio. Given these immunization successes, why is there continued interest in strategies to increase immunization levels? The three chief reasons relate to concerns about current immunization levels, costs, and the sustainability of the immunization delivery system.

Disease levels, while they are one of the chief outcomes of interest, are a late indicator of the soundness of the immunization system. **Immunization levels** are a better indicator than vaccine-preventable disease rates to determine if there is a problem with immunization delivery.

Concerns about U.S. immunization levels include:

Childhood immunization rates are still suboptimal. For example, in 2002 only 82% of children 19 to 35 months of age had received four doses of DTaP vaccine.

For other age groups, immunization rates are considerably lower. According to National Health Interview Survey data from 2002 (early release data) only 66% of people 65 years of age and older received the flu vaccine in the past twelve months and 56% of seniors had ever received pneumococcal vaccine.

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

Uptake is lagging for some antigens. For example, in 2002 81% of children had received varicella vaccine by their second birthday. Immunization rates in general seem to be lagging for healthcare workers. The 2002 National Health Interview Survey results indicate only 38% of healthcare workers received influenza vaccine in the previous year.

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 have been tapering off since 1997.

Cost effectiveness is also of great concern. We need to know which strategies increase immunization levels with the least expenditure so they can be prioritized.

Sustainable systems for vaccinating children, adolescents, and adults must be crafted. It has been recognized that high immunization rates cannot rest upon one-time or short-term efforts.

Why focus on strategies to increase immunization?

- Immunization levels are not optimal
- Cost effectiveness is a concern
- Sustainability is a concern

There is interest in understanding strategies to increase immunization levels in order to create lasting, effective immunization delivery systems.

MATCHING STRATEGIES TO EXISTING PROBLEMS

Matching Strategies to Existing Problems

- Value of a strategy depends on:
  - –implementation
  - –potential effectiveness
  - –how well it is matched to existing problems

Many available strategies work to increase immunization, but some do not. The value of a strategy depends upon its implementation, its potential effectiveness, and how well it is matched to existing problems. Some do not work because they are ill-conceived from the beginning. Some strategies do not work because they are implemented badly. Some are simply misdirected - they address the wrong problems.

School entry laws have been shown to effectively increase client demand for vaccines, although the effectiveness of other common strategies (*e.g.*, advertising) is less well documented. Similarly, there are proven strategies well suited to the problem of low access to immunization services (*e.g.*, reducing costs, WIC, home visiting).

When considering what new strategies to implement, proposed solutions must be carefully matched to current problems. At present in the U.S., most people have sufficient interest in and access to healthcare and are seen, at least periodically, in healthcare systems. Those that remain unvaccinated do so largely because healthcare practices and providers do not always perform optimally in delivering vaccines. So this chapter focuses on **immunization strategies for healthcare practices and providers.**

The purpose of the approach discussed below is to move healthcare personnel from a state of unawareness about the problem (low immunization rates in their practice) to one in which they are aware, concerned, and knowledgeable; motivated to change; ready to try new behaviors (strategies); and capable of sustaining the new behavior.

The acronym used by the National Immunization Program (NIP) for this approach is **AFIX: Assessment** of the immunization coverage of public and private providers; **Feedback** of diagnostic information to improve service delivery; **Incentives** (or recognition) for improved performance; and **eXchange** of information among providers. After discussing each of these steps, the chapter highlights specific practice-based strategies and details where to find more resources on this topic.

AFIX

Assessment
Feedback
Incentives
eXchange

THE AFIX APPROACH

OVERVIEW

Routine assessment and feedback of vaccination rates obtained at the provider site – whether public or private – is one of the most effective strategies for achieving high, sustainable vaccine coverage. Georgia was the first state to implement AFIX in all public clinics.

From 1986 to 1999 median series-completion rates among Georgia's public clinics for 4 DTPs, 3 polio vaccines, and 1 measles-containing vaccine (the 4:3:1 series) at 24 months of age increased from 40% to 91%. In a recent analysis of the Georgia public clinic experience, several factors were found to have significant positive influence on immunization rates: the lead nurse participated in the feedback session after assessments and received an incentive to raise clinic coverage; the site used a phone system for patient reminders, used WIC voucher incentives, and conducted home visits for children who fell behind in the series.

The Georgia experience is not unique. Other states and localities that have used AFIX strategies for three or more years have shown gradual and consistent improvement in public sector coverage levels. In a private sector study, involving pediatricians, the median up-to-date coverage for 4:3:1 at 24 months of age improved in participating practices from 78% at baseline to 87% at the second assessment. The Together for Tots program, a 10-state effort to improve immunization practices in Community/Migrant Health Centers using continuous quality improvement, saw levels rise from 54% to 84% for 4:3:1 between 1996 and 2000.

AFIX enjoys wide support. One of the Standards for Child and Adolescent Immunization Practices recently updated and revised by the National Vaccine Advisory Committee (NVAC) calls upon providers to do annual assessments of coverage levels. In 1996, following the success of the Georgia AFIX strategy, a congressional mandate was passed which stated that all grantees receiving federal funds for vaccination programs were required to conduct annual assessments of vaccination rates in all their public health clinics. The Advisory Committee on Immunization Practices (ACIP) issued a statement endorsing the AFIX process and recommending that it be used by all public and private providers. One of the goals in The Healthy People 2010 report emphasizes that 90% of immunization providers undergo assessments of childhood immunization level in their practices, a key component of AFIX, ever two years. In 1998, the American Academy of Pediatrics (AAP), the American Academy of Family Physicians (AAFP), state health department staff and pharmaceutical company representatives agreed that coverage assessments of private practices using the AAP and AAFP to help gain access was the most effective way of raising and sustaining immunization coverage.

AFIX is also an evidence-based strategy shown to improve vaccination coverage among adults. 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 widely disseminated compared to childhood AFIX, this strategy can be a powerful tool to improve rates among the adult population.

VFC - AFIX INITIATIVE

In order to extend the benefits of AFIX to private providers, which now vaccinate nearly 80% of children in the US, NIP launched an initiative in 2000 to incorporate measurement and feedback activities during Vaccines for Children (VFC) provider site visits. This initiative links AFIX with the VFC program and focuses on increasing vaccine management practices and immunization services within provider offices.

VFC is a federal program that purchases vaccines for eligible children who meet one of the following requirements: qualify for Medicaid, have no insurance, are Native American or Alaska Native, or have insurance but it does not cover immunizations (underinsured). Those children that are underinsured may receive VFC vaccines at Federally Qualified Health Centers (FQHC) or Community/Migrant Health Centers.

All states participate in this popular program, which serves approximately 44,000 provider sites, primarily in the private sector. The VFC program benefits providers as well as children by reducing cost as a barrier and encouraging children to stay in a medical home. VFC provider site visits are conducted to review compliance with VFC eligibility screening requirements and to evaluate vaccine storage and handling procedures. These VFC site visits provide an excellent opportunity to expand assessment and feedback activities in the private sector.

Special Characteristics of AFIX

- Focus on outcomes
- Focus on providers
- Both personal and technological

AFIX has some important characteristics that deserve emphasis.

Focus on outcomes – AFIX starts with assessment. Assessment data helps pinpoint the processes that need to be initiated or remedied. The AFIX approach helps providers focus on specific improvements.

Focus on providers - AFIX focuses on changing healthcare provider behavior. Strategies implemented do not have to be of a sweeping governmental scope, nor do they need to be attempts to change the hearts and minds of every individual client.

Both personal and technological - AFIX depends on the wholehearted, intense, and subtle union of technology (in the form of assessment methodology and diagnostics) with art (in the form of persuasive feedback, moving incentives, and stimulating exchange of information). Both the message and its delivery are critical to the success of the AFIX approach. An artful, dynamic delivery can be informative as well as motivational.

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 people as well as to provide targeted diagnosis for improvement. This step, along with feedback of the results, is essential because, while most healthcare

providers share the vision for high immunization rates, they do not see their own practice's immunization rates for what they really are. This lack of awareness has been documented in several studies showing that pediatricians greatly over-estimated the proportion of fully immunized children in their practices. Assessment increases awareness.

The primary assessment tool that CDC offers and supports is the Clinic Assessment Software Application (CASA) and the Adult Clinic Assessment Software Application (ACASA). In addition to the traditional Classic CASA methods, CDC has created two other assessment options which reduce the amount of time required to conduct an assessment in private provider offices: Mini-CASA and Hybrid CASA. The level of detail desired from the CASA reports will help guide the choice of an assessment method. (See Appendix B for a description of the 3 assessment methods: the Classic CASA, which requires a minimum of 100 records; the Mini-CASA, which requires 50 records; and the Hybrid CASA, which requires 30 records.)

The Classic CASA/ACASA and the Mini-CASA assessment methods provide detailed reports, which diagnose specific problems. For example, the report results could indicate whether children start their series on time, whether and when patients drop out of the system, whether recall is used effectively, whether vaccines are given simultaneously, and whether record keeping and documentation are adequate. The Hybrid CASA does not offer the same level of detailed reports, though it requires the least amount of time. Depending on the chosen assessment method and the organization of the medical records, the time spent reviewing immunization records and entering the immunization data into the software program could take between 2 and 8 hours.

CASA/ACASA are easy to use and can be downloaded from the NIP website (listed in the resource directory) or obtained on disc from NIP. There are many special features, including:

- error-checking to ensure that the immunization dates occurred after the date of birth, before the review date, and after the previous doses;
- capability of capturing useful, nonimmunization information by including data fields such as WIC, AFDC, Head Start, EPSDT, HEDIS information, and date of last visit;
- capability of exporting data to other software applications by saving to an ASCII text, dBase file, or an Excel spreadsheet;
- ability to generate a mailing list and a reminder or recall letter/postcard; and
- an easy to use sampling feature that shows the number of records that should be reviewed in order to achieve a statistically relevant estimate of vaccination levels if a fixed number of records, i.e., 100 for Classic CASA, 50 for Mini-CASA, and 30 for Hybrid CASA.

Tools for Assessment

- Classic CASA/ACASA
- Mini-CASA
- Hybrid CASA

Feedback

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

How to Provide Feedback

- To all who can make a change
- With feeling and precision
- Without judgment
- With confidentiality as appropriate
- As a challenge

- an ability to capture (in ACASA) high risk conditions including behavioral, medical, and occupational for those younger adults with indications to receive hepatitis B, influenza, or pneumococcal vaccine.

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 people who can make a change. Assessment together with feedback creates the awareness necessary for behavior change.

Strong evidence of the positive effects of provider feedback has been shown in a range of settings (private practice, managed care, public clinics and community health centers, academic, and VA settings), for a range of providers (resident and staff physicians, non-physician providers, internal medicine, family medicine, and general practice), for adults and children (although there are no completed studies to date on adolescents), and for most universally-recommended antigens.

Feed back the data to everyone who can make a change. The data should be presented to the entire team of people who can make a change – not only to policymakers, but also to policy implementers. In a practice, this includes the medical and nursing staff as well as the office manager and receptionist. It is best if they are all presented with the data simultaneously to minimize inter-professional blaming.

Feed back the data with feeling. Feedback is not a pale, passionless out-pouring of data. Well-designed feedback is tantalizing and challenging. The most effective "AFIXers" are those emotionally involved with the "FIX."

Feed back the data with precision. Data should not be sent to the healthcare providers without explanation or analysis. Within a CASA Summary Report there are data on immunization levels and there are more detailed diagnostic data. Diagnostics isolate a single component of immunization delivery and serve as clues to the source of the systemic problem. They include, for example, data on the percent of patient records that reflect clients who are "lost" (*i.e.*, eligible for vaccine, but not seen in the past year), who were not given all needed vaccines simultaneously on the last vaccination visit, or who "dropped-out" of the immunization schedule. (For more information on CASA reports, see "How to Read a CASA Summary Report: Just for Starters" in Appendix B.)

Because of the diagnostic capabilities of CASA, one does not need to "fish around," asking a practice if they implement this strategy or that. For example, a practice with a 50% drop-off rate need not be asked if they have an effective recall system. We know by the

data what the office is (not) doing or how (in)effectively they are doing it. Once you have established the accuracy of the method, the only issue that remains to be discussed is how to best improve those specific areas that are below the norm.

Feed back the data as data, not as judgment. There are no bad people, only bad systems. That is, the problem is not the individuals employed at the site, it is their immunization delivery system. You need not scold the people, just help them improve the system.

Feed back the data with respect for confidentiality. The acceptance of an outside assessor depends upon trust that the data will be used in a pre-arranged, circumscribed way. Don't violate that trust.

Feed back the data as a challenge. The dedication to confidentiality should never be compromised. However, in some circumstances, offices agree to allow their data to be used publicly, either in association with their name or not. By comparing an office's immunization rates with national goals or, preferably, with the rates of peers, competitive spirit can be stirred. Those at the top struggle to keep or attain first place; those at the bottom scramble to avoid last place. Graphic representation of relative standing – such as comparing providers anonymously – is useful, as is wide public dissemination of the assessment results, *when appropriate*.

Incentives and Recognition

Incentive
- Extrinsic reward
- Something that incites to action

Recognition
- Special notice or attention
- Powerful motivator

INCENTIVES AND RECOGNITION

People who enter the healthcare profession are likely to be motivated by an intrinsic desire to prevent disease and its complications. Immunization is primarily dependent upon this intrinsic motivation. However, as a supplement, extrinsic rewards, or incentives, are often useful. It should be noted that incentives will not overcome significant barriers (*e.g.*, if your practice loses $15 every time you vaccinate someone, framed certificates of appreciation are unlikely to sway you to immunize).

An *incentive* is something that incites or has a tendency to incite to determination or action. This necessitates prearranged performance standards ("if I do X, I will get Y"). *Recognition* is special notice or attention, and is a powerful motivator. Prearranged performance standards are not necessary for recognition. When a recognition program has been in place for a while, people begin to expect it, so it becomes, in a sense, an incentive program.

What Makes An Incentive Useful

- Based on fair, credible assessment
- Positive
- Timely
- All levels of involved personnel
- Reflect desired outcomes or process
- Related to mission

What makes an incentive useful? Incentive programs should:

- Reward achievement on the basis of a **fair, credible, well-communicated assessment.**
- **Be positive;** the motivating effect of carrots exceeds the motivating effect of sticks.
- Reward achievement in a **timely** fashion.

- Offer **something the individual values.** Not everyone values the same things, so discuss the incentives in advance of kick-off.

- Professional recognition is often motivating. Food is (almost) always motivating. Money is 'iffy': it may be motivating, but it may be insulting or encourage cheating.

- **Be aimed to all levels of involved personnel** (e.g., clerical and nursing staff).

- **Create team spirit** and/or utilize the competitive nature of Americans.

- **Be publicized.** When a professional shares his/her success story with another professional, you make two friends. Having it in writing seems quite powerful.

- **Reward achievement of attainable goals.** Incremental goals help; complicated goals don't.

- **Reflect desired outcomes** (*e.g.*, immunization rates) or process (e.g., putting a reminder system in place) or both. "Most improved" is a useful category to keep everyone in the running.

- **Be inexpensive** because these are usually more sustainable.

- **Be related to mission** (*e.g.*, the reward for letting us do a CASA is that at the end we'll give you a list of children at your practice who are behind on immunizations).

- **Create a bond** between the public and private sectors *(e.g.*, the prize for letting us do an assessment is that at the end we'll call the children at your practice who are behind on immunizations).

- NOT dictate methods. Leave the innovation about "how to" up to the practice. Of course, you can be there as a resource if they have questions or want suggestions.

- NOT be stale ("Been there, won that.")

- NOT reward winners with more unwelcome work.

The costs of an incentive program may be shared with other immunization and/or community partners. Various organizations and private enterprises are available to help fund creative incentive ideas. For example, local professional organizations may allocate space in their newsletter to acknowledge immunization accomplishments. Businesses, service organizations, or vaccine manufacturers may wish to donate food, gifts, gift certificates, and/or plaques for an awards luncheon or banquet. A well-known public official or immunization advocate may be willing to hand out achievement awards at a meeting. Finally, continuing education credit could be offered at meetings at which the assessment program is discussed.

Incentive Options

- Plaque or memo of appreciation
- Article of recognition in health department or professional organization newsletter
- Luncheon for office staff
- Provision of continuing education

eXchange of Information

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

eXchange OF INFORMATION

When healthcare providers have moved from being unaware of their site's low immunization rates to being aware, concerned, and knowledgeable as well as motivated to change, they are then ready to try new strategies. The exchange of information among healthcare providers is an important next step because peer education is the best way to learn what new strategies to try.

Why should the exchange of information among providers be supported? Discussion with fellow workers or education from peers seems to help most adults learn new things, or recognize they need to stop doing old things. This exchange helps to educate, motivate, and coordinate in a way that is powerful because it is believable and relevant.

- **Education.** The exchange of information gives people access to more experience than they have time to accumulate individually. People learn from their peers what strategies work and what strategies don't. The educational aspect of these conversations can dispel myths and negative attitudes (*e.g.*, inflated coverage estimates, the number of shots that parents will accept), clarify true contraindications, and foster better understanding of assessment data as a diagnostic tool. During the cross-pollination some new ideas may even be generated.

- **Motivation.** By publicly acknowledging success, providers are informed of the shifting norm. This stimulates competition and motivates improvement which, in turn, establishes the need for follow-up assessments. The exchange of information about practices' relative immunization rates is an incentive to change.

- **Coordination.** Once the participants' common mission to prevent disease has been clarified, people may begin to see how they can use and share common resources, improve communication within and between practices, and, possibly even coordinate with the registry and public health department. Increased communication often leads to improved rapport.

What forums are appropriate for exchange among providers? Meetings of healthcare providers may be state-wide, regional, or local. They may be convened solely with the practice members - physicians, nurses, office managers, and clerical staff - or with sections of professional organizations such as the American Academy of Pediatrics, American Academy of Family Physicians, American Nursing Association, or the Public Health Association. Meetings of healthcare providers within a managed care plan are another excellent setting for this kind of exchange. Award ceremonies serve as a particularly pleasant and supportive forum to open the exchange.

What type of information should be exchanged among providers? Information on both immunization levels and on the process of increasing immunization levels should be exchanged. Sharing

eXchange of Information

- Choose the appropriate forum for exchange of information
- Exchange information on both immunization levels and process of increasing levels
- Peer reports are usually more influential than official reports

information on immunization levels - whether that is limited *(e.g.*, coverage levels, rank ordered by the type of service to increase comparability if possible) or more extensive (*e.g.*, specific antigen coverage levels, drop off levels, non-simultaneous vaccination levels) - will keep the group focused on the desired end-point. Data can be presented as blinded coverage levels or comparing a provider's rates to an anonymous average or an anonymous bar graph of other provider coverage rates. Sharing data on the process of getting there will confirm that providers are establishing sustainable systems. If awards are given, a category for "most improved" keeps even late bloomers in the running.

Peer reports are usually more influential than official reports. Peer reports on their successful documentation methods, vaccination practices, and office protocols are often interesting. Discussions of processes used in practices to educate staff and to streamline procedures are also useful. Information on true vaccine contraindications, ACIP recommendations, the Standards for Child and Adolescent Immunization Practices, and the Standards for Adult Immunization Practices should supplement peer reports, but they are often too dry to stand alone. Testimonial success stories are useful to show that, while we all start out flawed, improvement is an attainable goal. Indeed, almost all practices can be made better by better practices.

Strategies for High Immunization Levels

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

BETTER PRACTICES

What are the strategies that lead to high immunization levels in a practice? In this section we will discuss well-studied strategies that are applicable within most public and private sector practices. Additionally, we will discuss some strategies that simply enjoy tremendous intuitive appeal (*e.g.*, good immunization records). The strategies are summarized under the following headings:

- Records that are accurate, understandable, and available
- Recommendations to parents and reinforcement of the need to return
- Reminder and recall messages to patients
- Reminder and recall messages to providers
- Reduction of missed opportunities
- Reduction of barriers to immunization within the practice

Records

- Must be easy to read
- Must be available at the time of the visit
- Must be accurate
  - –reflect who is in the practice
  - –reflect all vaccines given

It has been noted anecdotally that many healthcare practices that successfully implement these strategies do so because there is an Immunization Champion among them. Immunization Champions are highly motivated and find creative ways to solve problems.

RECORDS THAT ARE ACCURATE, UNDERSTANDABLE, AND AVAILABLE

Easy-to-read immunization records that are available at the time of the visit are essential. Adult medical records often lack a front sheet that reflects the important preventive services. Pediatric patients often have a front sheet from which one cannot, at a

glance, assess age-dependent immunization status. Putting in place a system that ensures the front sheet is kept current also helps.

Immunization records must be accurate. The active medical records must reflect who is actually in the practice. Charts of people who have moved or are going elsewhere for services should be clearly marked accordingly or removed. Conversely, charts should not be archived simply because a patient has not presented for a prolonged time.

Patients often receive vaccines at more than one provider office, so communication between sites is needed to produce complete and accurate immunization records. Specifically, it is important for school-based, public health, and community-based immunization sites to communicate with primary care personnel through quick and reliable methods (*e.g.*, telephone, fax, and, if possible, email). Someday immunization registries may make this communication seamless. We should work toward, but not wait for, this day to implement efficient communication between vaccine providers. Unfortunately, the effectiveness of patient-held records on immunization rates is difficult to estimate because of the small number of studies, limitations in study design, and inconsistent results.

Recommendations and Reinforcement

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

RECOMMENDATIONS TO PARENTS AND REINFORCEMENT OF THE NEED TO RETURN

The recommendation of a healthcare provider is a powerful motivator. One study demonstrated that when the healthcare provider's opinion of influenza vaccine was positive, even adults whose initial opinion of influenza vaccination was negative were likely to receive the vaccine. Similarly, other work has shown that parents of pediatric patients are very likely to follow vaccine recommendation of the child's doctor.

It has been found that, irrespective of true immunization status, most parents believe their child is fully vaccinated. Parents may not have been told or may not have understood that return visits were necessary. Anecdotally, patients often find it useful to have the next appointment date in hand upon departure from the current visit. As a supplement to this, the timing of the return visit can be linked to some calendar event (*e.g.*, "Return for your next flu vaccine in a year, right before Halloween." "Your child will need her next set of vaccines in two months. That's her 6-month birthday...right after Valentine's day.")

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

REMINDER AND RECALL MESSAGES TO PATIENTS

Definitions. Patient reminders and recall messages are messages to patients or their parents that recommended immunizations are due soon (reminders) or past due (recall). The messages vary in their level of personalization and specificity and in their medium (*e.g.*, postcard, letter, telephone) and their degree of automatization.

Reminders and Recall to Patients

- Reminders and recall are effective
- Do not have to be expensive, elaborate, or computerized
- Support for wide-spread usage
- May increase utilization of other preventive measures

The effectiveness of patient reminders and recall. Both reminders and recall have been found to be effective in increasing attendance at clinics and improving vaccination rates in various settings. This is probably because multiple healthcare visits usually are needed for patients to be fully vaccinated and these visits are sometimes missed. Clients can be quite variable in their attendance for vaccination appointments.

During the past 20 years, many studies of the effectiveness of mail or telephone appointment reminders/recall have shown consistently important increases in patient compliance for vaccination as well as a variety of other scheduled health visits. Generally, mail and telephone reminders are equally effective.

Costs. Many health providers have been reluctant to institute aggressive reminder/recall systems because of perceived costs. Tracking systems that generate reminder and recall messages do not have to be expensive, elaborate, or computerized. A card-file box with weekly dividers can work as a tickler system.
In many provider settings, the costs of establishing an aggressive notification system may be minimized by the use of automated dialing technology (autodialers). In a recent study conducted by CDC NIP and the Colorado Immunization Program, computer-generated telephone calls and letters resulted in a 14% increase in immunization coverage at a cost of $5.37 per child after start-up.

Support for and wide-spread usage of patient reminders and recall. 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. The Advisory Committee on Immunization Practices 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

Immunization and beyond: additional benefits of patient recall and reminder systems. Three trials conducted by the National Immunization Program and the Georgia Department of Human Resources have demonstrated that computer-generated telephone reminders and recall messages, in addition to positively affecting the "on-time" rate of immunizations, bring a significant number of children who have dropped out back into the public health delivery system. Studies in the private sector show that a key benefit of patient reminder/recall systems is that they increase utilization of other preventive measures. We are not improving one preventive measure at a cost to the others. When we institute patient reminder and recall systems for immunization, we increase tuberculosis, lead, and anemia screening. Improvements in one system leads to improvement in others.

REMINDER AND RECALL MESSAGES TO PROVIDERS

Provider reminders and recall messages are communications from healthcare personnel (or computers) to healthcare providers that, for individual clients, routine immunizations are due soon (reminders) or past due (recall). 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 include:

- a computer-generated list that notifies a provider of the children past-due for vaccines who are to be seen that clinic session,
- a red note "No Pneumococcal Vaccine on Record" that a receptionist stamps on a senior's chart where the nurse will write the vital signs,
- an "Immunization Due" clip that a nurse attaches to the chart of an adolescent who has not had hepatitis B vaccine.

The content of the provider reminders and recall messages vary as do the techniques to deliver them. To be effective, the information must be conveyed to the provider before or at the time of the patient's office visit. Some offices have found that it is productive to have one knowledgeable and determined "gate keeper" who checks and updates immunizations at each visit.

Provider reminders and recall systems have been found to be effective in increasing immunization levels when used alone or in combination with related strategies such as provider education or patient recall.

REDUCTION OF MISSED OPPORTUNITIES TO VACCINATE

Definitions. 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 settings that routinely offer immunization, such as primary care offices or public health clinics, and settings that do not routinely offer immunizations including healthcare settings (*e.g.*, emergency departments, inpatient wards) and public health settings (*e.g.*, WIC program sites).

Why are there missed opportunities to vaccinate? Many nurses and physicians avoid simultaneous administration of four or even three injectable vaccines. Frequently stated reasons for resistance to simultaneous administration have included concern about reduced immune response, adverse events, and parental objection. These sources of resistance 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).

Missed Opportunity

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

Settings Where Missed Opportunities Occur

- Settings that traditionally offer immunizations (e.g., primary care offices or public health clinics)
- Settings that do not traditionally offer immunizations
  - –healthcare settings (e.g., ED)
  - –public health settings (e.g., WIC)

Causes of Missed Opportunities

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

Strategies for Reducing Missed Opportunities

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

Reduction to Barriers to Immunization

- Physical barriers
  - –waiting time
  - –distance
- Psychological barriers
  - –discourtesy
  - –criticism

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

Strategies to rid practices of missed opportunities. Several studies have shown that eliminating missed opportunities could increase coverage by up to 20 percent. Strategies designed to rid practices of missed opportunities have included several modalities alone or in combination. Examples include:

- **Standing orders** – These are interventions in which non-physician immunization personnel vaccinate clients by protocol without direct physician involvement at the time of the immunization. This may occur in a variety of settings such as clinics, hospitals, and nursing homes. When used alone or in combination with other interventions, standing orders have had positive effects among adults in a range of settings.

- **Provider education** – Giving immunization providers information has been attempted with written materials, videos, lectures, and computerized software. Providing only knowledge may have limited impact on provider behavior, while implementing multicomponent interventions that incorporate both knowledge and other strategies (*e.g.*, feedback, incentives) show more convincing evidence of effectiveness.

- **Provider reminder/recall systems** – These are discussed above. While provider reminder/recall systems generally work to increase immunization levels, they may not be effective in decreasing missed opportunities if they are implemented in an inconsistent way or if providers strongly adhere to invalid contraindications.

REDUCTION OF BARRIERS TO IMMUNIZATION WITHIN THE PRACTICE

Time and space are two of the chief barriers to vaccination. Attempts have been made to decrease the distance people must travel or the time they must spend to get vaccinated. Expanding hours or access in clinical settings is one example of this approach. Although data are insufficient to support such an intervention by itself, strong evidence exists that this intervention is a valuable component of a multicomponent intervention.

Psychological barriers to healthcare are often more subtle, but may be just as important. Unpleasant experiences (*e.g.*, fear of immunizations, being criticized for previously missed appointments, difficulties leaving work for a clinic appointment) may lead clients to procrastinate about receiving needed vaccination. Health care practices should provide a supportive and safe atmosphere for

clients.

SUMMARY

Immunization delivery systems must be improved for people in all age groups, and especially for the poor and minorities. Strong evidence exists that this improvement can be achieved through practice-based assessment of immunization rates and feedback of those rates to all the people involved. The use of incentives - even if they are simple recognition of a good job - are useful for enhancing motivation. The exchange of information among providers is useful for maintaining motivation, as well as for aiding education and coordination. The facilitators of this exchange should encourage discussion of immunization levels, but also of the system changes that lead to improved immunization levels.
We have to get out the word that we have strong evidence about what system changes are needed. We have to get out the word that there are benefits beyond increased immunization rates; these system changes can lead to improvement in a wide range of clinical prevention services. And we need to find (or become) the prevention Champions who will lead the work of improving immunization records, recommending vaccines, creating aggressive reminder and recall systems, and ridding practices of immunization missed opportunities and barriers. We know we can do it and our children and our parents deserve it.

Guide to Community Preventive Services

- Evidence-based source on strategies
- For more information
  - –Email epogda@cdc.gov
  - –http://www.thecommunityguide.org/

THE GUIDE TO COMMUNITY PREVENTIVE SERVICES

This chapter has benefitted considerably from the Guide to Community Preventive Services, the definitive, evidence-based source on strategies to increase immunization levels. The Guide, developed under the auspices of the U.S. Public Health Service, summarizes data on the effectiveness and, when possible, the cost-effectiveness of population-based interventions for prevention and control. The Guide provides recommendations on these population-based interventions and methods for their delivery. The Guide's chapter on vaccine preventable disease provides information about a wider range of strategies to improve coverage than are included here and provides more of the evidence on which some of the conclusions in this chapter are based.

SELECTED REFERENCES

CDC. Programmatic strategies to increase vaccination rates - assessment and feedback of provider-based vaccination coverage information. *MMWR* 1996; 45:219-220.

CDC. Recommendations of the Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics, and the American Academy of Family Physicians: Use of reminder and recall by vaccination providers to increase vaccination rates. *MMWR* 1998; 47:715-717.

Dietz VJ, Baughman AL, Dini EF, Stevenson JM, Pierce BK, Hersey JC. Vaccination practices, policies, and management factors associated with high vaccination coverage levels in Georgia public clinics. *Arch Pediatr Adolesc Med* 2000; 154:184-189.

Dini EF, Linkins RW, Sigafoos, J. The impact of computer-generated messages on childhood immunization coverage. *Am J Prev Med* 2000; 18(2):132-139.

LeBaron CW, Chaney M, Baughman AL, Dini EF, Maes E, Dietz V, Bernier R. Impact of measurement and feedback on vaccination coverage in public clinics, 1988-1994. *JAMA* 1997; 277:631-635.

LeBaron CW, Mercer JT, Massoudi MS, Dini EF, Stevenson JM, Fischer WM, Loy H, Quick LS, Warming JC, Tormey P, DesVignes-Kendrick, M. Changes in Clinic vaccination coverage after institution of measurement and feedback in 4 states and 2 cities. *Arch Pediatr Adolesc Med* 1999; 153: 879-886.

Lieu T, Black S, Ray P. Computer-generated recall letters for underimmunized children: how cost-effective? *Pediatr Infect Dis J* 1997; 16:28-33.

Lieu T, Capra A, Makol J, Black S, Shinefield H. Effectiveness and cost-effectiveness of letters, automated telephone messages, or both for underimmunized children in a health maintenance organization [Abstract]. *Pediatrics* 1998; 101:690-691.

Massoudi MS, Walsh J, Stokley S, Rosenthal J, Stevenson J, Miljanovic B, Mann J, Dini E. Assessing immunization performance of private practitioners in Maine: impact of the Assessment, Feedback, Incentives, and eXchange (AFIX) Strategy. *Pediatrics*, 1999; 103: 1218-1223.

National Vaccine Advisory Committee. Standards for Child and Adolescent Immunization Practices. *Pediatrics* 2003;112:958-63.

Poland GA, Shefer AM, McCauley M, et al. Standards for Adult Immunization Practices. *Am J Prev Med* 2003;25:144-150.

Yawn BP, Edmonson L, Huber L, Poland GA, Jacobson RM, Jacobsen SJ. The impact of a simulated immunization registry on perceived childhood immunization status. *Am J Man Care* 1998; 4:186-192.

This chapter describes how vaccines licensed for use in the U.S. are monitored for safety, and presents general information about the provider's role in immunization safety. For more information about contraindications and precautions, such as pregnancy and immunosuppression, refer to the General Recommendations on Immunization chapter, p. 13, and to Appendix A. Specific information about adverse events and contraindications for each vaccine may be found in the appropriate chapters.

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 effective. While almost all known vaccine adverse events are minor and self-limited, some vaccines have been associated with very rare, but serious health effects. The following key considerations underscore the need for an active and ongoing vaccine safety program.

DECREASES IN DISEASE RISKS

Today, vaccine-preventable diseases are at or near record lows. By virtue of their absence, these diseases are no longer a reminder of the benefits of vaccination. At the same time, approximately 10,000 cases of adverse events following vaccination are reported in the U.S. each year (these include both true adverse reactions and events that coincidentally occur after vaccination). This number exceeds the current reported incidence of vaccine-preventable childhood diseases. As a result, parents and providers in the U.S. are more likely to know someone who has experienced an adverse event following immunization than they are to know someone who has experienced a reportable vaccine-preventable disease. Thus, the success of vaccination has led to increased public attention on health risks associated with vaccines.

PUBLIC CONFIDENCE

Maintaining public confidence in immunizations is critical for preventing drops 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 1980's resulted in decreased vaccine coverage levels and the return of epidemic disease in Japan, Sweden, United Kingdom and several other countries. In the U.S., similar concerns led to increases both in the number of lawsuits against manufacturers and the price of vaccines, and 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.

Importance of Vaccine Safety

- Decreases in disease risks and increased attention on vaccine risks
- Public confidence in vaccine safety is critical
- Low tolerance for vaccine risks
  - Higher standard of safety is expected
  - Vaccinees generally healthy (vs. ill for drugs)
  - Lower risk tolerance = need to search for rare reactions

Comparison of Maximum and Current Reported Morbidity, Vaccine-Preventable Diseases and Vaccine Adverse Events, United States

Disease	Pre-vaccine Era*	2002**	% change
Diphtheria	175,885	1	99.99
Measles	503,282	37	99.99
Mumps	152,209	238	99.80
Pertussis	147,271	8,296	94.40
Polio paralytic)	16,316	0	100.00
Rubella	47,745	14	99.97
Cong. Rubella Synd.	823	3	99.60
Tetanus	1,314	23	97.90
H.*Influenzae* type b and Unknown (< 5 yrs)	20,000+	282	98.60
Total	1,064,854	8,894	-99.16
Vaccine Adverse Events	0	14,199^	+++

* Maximum cases reported in pre-vaccine era and year
\+ Estimated because no national reporting existed in the prevaccine era
^ Adverse events after vaccines against diseases shown on Table =7,773
** Provisional (01/06/2003)

LOW TOLERANCE FOR VACCINE RISKS

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 products administered to persons who are already sick. This lower risk tolerance for vaccines translates into a need to investigate the possible causes of very rare adverse events following vaccinations; a frequency of side effects that would be acceptable for other pharmaceutical products.

WIDESPREAD AND MANDATED USE OF VACCINES

Importance of Vaccine Safety

- **Vaccinations universally recommended or mandated**
- **Ongoing safety monitoring needed for the development of sound policies and recommendations**

Vaccines must also meet the highest standards of safety because almost all children in the U.S. are immunized. Not only do most parents immunize their children to protect them against vaccine-preventable diseases, but immunization is also mandated under many state and local school entry requirements. Because of this widespread use, safety problems with vaccines have the potential to impact a large number of people. 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 U.S. by the Food and Drug Administration (FDA).

SOUND IMMUNIZATION RECOMMENDATIONS AND POLICY

In a context in which risks of contracting vaccine-preventable diseases are low, the risks of vaccine side effects, especially the very small chance of serious adverse effects, take on greater weight and need to be continually reevaluated. 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, for example, in the U.S. with smallpox and oral polio vaccines as disease neared global eradication. Complications associated with each vaccine exceeded the risks of the diseases, leading to discontinuation of routine smallpox vaccinations in the U.S. (prior to actual global eradication) and a shift to a safer inactivated polio vaccine. Sound immunization policies and recommendations affecting the health of the nation depend upon the ongoing monitoring of vaccines and continuous assessment of immunization benefits and risks.

METHODS OF MONITORING VACCINE SAFETY

PRELICENSURE

Vaccines, like other pharmaceutical products, undergo extensive safety and efficacy evaluations in the laboratory, in animals, and in

sequentially-phased human clinical trials prior to licensure. Phase I human clinical trials usually involve anywhere from 20 to 100 volunteers and focus on detecting serious side effects. Phase II trials generally enroll hundreds of volunteers. These trials might take a few months, or last up to three years. Safety is still an important focus, but now tests are also charting how the human immune system responds to the vaccine. At this time, the vaccine is fine-tuned. Phase II trials set the most effective use of the vaccine, the best dose for effectiveness and safety and the right number of doses. Next, the vaccine moves into phase III trials. Phase III vaccine trials 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 to 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 its 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 (10,000's persons) are inadequate to assess the vaccine's potential to induce 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 (GMP) with prerelease 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.

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 pre-existing conditions that may promote reactions
- identify whether there are particular vaccine lots with unusually

Prelicensure Vaccine Safety Studies

- Laboratory
- Animals
- Humans

Prelicensure Human Studies

- Phases I, II, II trials
- Common reactions are identified
- Vaccines are tested in thousands of people before being licensed and allowed on the market
- Poorly detected reactions:
  - Rare
  - Delayed onset
  - Subpopulations

Postlicensure Surveillance

- Identify rare reactions
- Monitor increases in known reactions
- Identify risk factors for reactions
- Identify vaccine lots with increased rates of reactions
- Identify signals

Postlicensure Vaccine Safety Activities

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

high rates or types of events

- identify signals of possible adverse reactions which may warrant further study or effect current immunization recommendations.

Historically, postlicensure monitoring of vaccine safety has relied on healthcare providers and the public to report side effects and "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 (LLDB)'s have been added to improve our capabilities to study rare risks of specific immunizations. Phase IV studies can be an FDA requirement for licensure. These trials include volunteers in the 10,000s and may address questions of long-term effectiveness and safety or examine unanswered questions identified in Phase III clinical trials. Most recently, a clinical evaluation network has been established which will increase our understanding of vaccine reactions at the individual, "patient" level.

THE VACCINE ADVERSE EVENT REPORTING SYSTEM (VAERS)

Vaccine Adverse Event Reporting System (VAERS)

- Jointly administered by CDC and FDA
- National reporting system
- Passive (depends on health care providers and others to report)
- Receives ~10,000 reports per year

The National Childhood Vaccine Injury Act of 1986, mandated that healthcare workers who administer vaccines, and licensed vaccine manufactures, report certain adverse health events following specific vaccinations. The Vaccine Adverse Event Reporting System (VAERS) is a national reporting system, jointly administered by the CDC and FDA. VAERS was created in 1990 to unify efforts for 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 10,000 reports per year (>130,000 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 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. In a review of VAERS from 1991-2001, reports are received from manufacturers (36.2%); health care providers (20%); state and local health departments (27.6%); patients or parents (4.2%); others (7.3%) and unknown (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, and the person reporting the event. According to FDA regulations, serious 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 and/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 MMR vaccine caused by gelatin allergy. Additional studies are always required to confirm "signals" detected by VAERS (because not all events are causally related to vaccine), but the system remains the cornerstone of postlicensure safety surveillance efforts. More information about VAERS, including the ability to report online can be obtained from the VAERS website at http://www.vaers.org or by calling the VAERS information line at 800-822-7967.

Vaccine Adverse Event Reporting System (VAERS)

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

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

ADVERSE EVENT CLASSIFICATIONS AND ASSESSMENT OF CAUSALITY

Adverse events following vaccination can be classified by frequency (common, rare), extent (local, systemic), severity (hospitalization, disability, death), causality, and preventability (intrinsic to vaccine, faulty production, faulty administration). A recent classification divides vaccine adverse events as follows:

Adverse Event Classification

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

- **Vaccine-induced:** due to the intrinsic characteristic of the vac cine 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 for some people to suspect vaccine to be the cause when a health problem occurs following vaccination, but in reality a causal association may or may not exist. Simply because a health problem occurred after vaccination does not mean that vaccination

caused the health problem; more information is 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 vs. unvaccinated (control) groups, and 7) a finding linking an adverse event to vaccine has been confirmed by other studies.

LARGE-LINKED DATABASES (LLDB)

Historically, when a signal of a potential vaccine safety concern was generated from passive surveillance, further ad hoc studies were needed to test the hypothesis. Such studies, while potentially informative about vaccine causality, were costly, time-consuming, and usually limited to assessment of a single event. The need to improve postlicensure monitoring of drug safety became widely recognized following the thalidomide incident. Faced with the inability of passive surveillance systems to establish causal relationships, and the lack of timeliness of ad hoc studies, pharmacoepidemiologists during the 1980s began to turn to large databases linking computerized pharmacy prescription (and later, immunization records) and computerized medical records. These LLDBs are derived from defined populations such as members of health maintenance organizations (HMOs), single-provider healthcare systems, and Medicaid programs. As these databases are usually generated in the routine administration of such programs and do not require completion of a vaccine adverse event reporting form, the problems of under-reporting or recall bias are reduced. Therefore, LLDBs can potentially provide an economical and rapid means of conducting postlicensure studies of safety of drugs and vaccines. CDC's Vaccine Safety Datalink (VSD) project is one example of such a system. It links the immunization and medical records on members of 8 HMOs, totalling >2.5% of the US population for various vaccine safety studies. For more information about Large link databases go to http://www.cdc.gov/nip/vacsafe.

Vaccine Safety Datalink

- Large-linked database
- Links vaccination and health records
- Population under "active surveillance"
  - 8 HMOs
  - >2.5% of the U.S. population
- Powerful tool for monitoring vaccine safety

CLINICAL IMMUNIZATION SAFETY ASSESSMENT (CISA) 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 will closely evaluate individuals who have experienced select adverse health events following vaccination. The

Clinical Immunization Safety Assessment (CISA) Network

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

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 existed in the US that investigated and managed vaccine side effects on an individual level for the purposes of providing patient care and systematically collecting and evaluating the experiences.

Established in 2001, the CISA network consist of 7 centers of excellence with vaccine safety expertise in partnership with CDC. These centers include Johns Hopkins University and the University of Maryland, in Baltimore, MD; Boston University Medical Center in Boston, MA; Columbia Presbyterian Hospital in New York City, NY; Vanderbilt University in Nashville, TN; Northern California Kaiser in Oakland and Stanford University in Palo Alto, CA. 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 vaccine (DPT). 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. In order 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 people 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 which summarizes the adverse events associated with vaccines. This table was developed by a panel of experts who reviewed the medical literature and identified the serious adverse events that are reasonably certain to be caused by vaccines. The Vaccine Injury Table was created to justly compensate those possibly injured by vaccines while separating out unrelated claims. As more information becomes available from research on vaccine side effects, the Vaccine Injury Table is amended. The Vaccine Injury Table can be found in Appendix F.

The VICP has received more than 5,000 claims since its effective date of October 1, 1988, 85 percent of which are for vaccines administered prior to the effective date (retrospective claims).

Vaccine Injury Compensation Program

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

See Appendix F-15

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 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-risk communication

VICP has achieved its policy goals of providing compensation to those injured by rare adverse events and liability protection for vaccine manufacturers and administrators. For more information about the VICP, visit their website at http://www.hrsa.gov/osp/vicp/vicp.html.

THE IMMUNIZATION PROVIDER'S ROLE

Federal regulations require vaccines to undergo years of testing before they can be licensed. Once in use, vaccines are monitored continually for safety and efficacy. Immunization providers also play a key role in helping to ensure the safety and efficacy of vaccines 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 patient/parent education about vaccine benefits and risks.

VACCINE STORAGE AND ADMINISTRATION

In order to achieve the best possible results from vaccines, immunization providers should carefully follow the recommendations for storage, handling, and administration found in each vaccine's package insert. Other steps to help ensure vaccine safety include: 1) inspecting vaccines upon delivery and monitoring refrigerator and freezer temperatures to assure 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. See Appendix D for more information on vaccine storage and handling.

TIMING AND SPACING

The 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 vaccines antibody response. For more specific information on timing and spacing of vaccines see chapter 2. A table on recommended minimum ages and intervals between vaccine doses can be found in appendix A.

Providers should also remember:

- 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. Such reactions are thought to result from the formation of antigen-antibody complexes.

- 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, like pediatric diphtheria and tetanus, produce increased rates of side effects when given too frequently. Good record keeping, maintaining careful patient histories, and adherence to recommended schedules can decrease the chances that patients receive extra doses of vaccines.

CONTRAINDICATIONS AND PRECAUTIONS

Contraindications and precautions to vaccination indicate when vaccines should not be given. A contraindication is a condition in a patient 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 patient that *may* increase the chance of a serious side effect or compromise the ability of the vaccine to produce immunity. Normally, vaccination is deferred when a precaution is present. However, 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. The CDC Guide to Contraindications to Childhood Vaccinations summarizes current recommendations in a handy booklet. It can be ordered on-line at http://www.cdc.gov/nip. More information about contraindications can be found in the contraindications/precautions table in appendix A and in 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 Appendix A. Many conditions are often inappropriately regarded as contraindications to vaccination. For example, in most cases, the following are **not** considered contraindications:

- Mild acute illness (e.g., diarrhea and minor upper-respiratory

Contraindication

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

Precaution

- **A condition in a recipient which may increase the chance or severity of an adverse reaction, or**
- **May compromise the ability of the vaccine to produce immunity**

Invalid Contraindications to Vaccination

- Mild illness
- Mild/moderate local reaction or fever following prior dose
- Antibiotic therapy
- Disease exposure or convalescence
- Pregnancy in the household
- Premature birth
- Breastfeeding
- Allergies to products not in vaccine
- Family history unrelated to immunosuppression

tract illnesses, including otitis media) with or without low-grade fever
- Mild to moderate local reactions and/or low-grade or moderate fever following a prior dose of the vaccine
- Current antimicrobial therapy
- Convalescent phase of illness
- Recent exposure to infectious disease
- Premature birth
- Breastfeeding

MANAGING VACCINE SIDE EFFECTS

Providers should use their best clinical judgment on 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 1 case for every 1.5 million doses of vaccine. Any provider who administers vaccines should have procedures in place and be prepared for emergency care of a person who experience an anaphylactic reaction. Any provider who administers vaccines should have procedures in place for the emergency care of a person who experiences an anaphylactic reaction. Epinephrine and equipment for maintaining an airway should be available for immediate use. All vaccine providers should be familiar with the office emergency plan, and should be certified in cardiopulmonary resuscitation.

REPORTING SUSPECTED SIDE EFFECTS TO VAERS

Healthcare providers are encouraged to report suspected vaccine reactions to VAERS through their website at http://www.vaers.org or by calling the VAERS information line at 1-800-822-7967. When providers report suspected vaccine reactions to VAERS, they provide valuable information that is needed for the ongoing evaluation of vaccine safety. The 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

Benefit and Risk Communication

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

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*, must be provided by all public and private vaccination providers before each dose of vaccine. Copies of Vaccine Information Statements are available from state health authorities responsible for immunization, or they can be obtained from CDC's National

Immunization Program website at http://www.cdc.gov/nip. Translations of Vaccine Information Statements into languages other than English are available from certain state immunization programs and from the Immunization Action Coalition website at http://www.immunize.org.

Healthcare providers should anticipate that some parents or patients may have questions 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 in dealing with vaccine safety concerns when they arise is imperative for vaccination providers.

Each person understands and reacts to vaccine information on the basis of different factors, including prior experience, education, personal values, method of data presentation, perceptions of the risk for disease, perceived ability to control those risks, and their risk preference. Some people may also be exposed to inaccurate information about vaccine risks through the media and Internet sites. Healthcare professionals can help by assessing patient's specific concerns and information needs, providing them with accurate information, and referring them to credible sources for more information.

When a parent or patient initiates discussion regarding a vaccine concern, the healthcare professional should discuss the specific concerns and provide factual information, using language that is appropriate. Effective, empathetic vaccine risk communication is essential in responding to misinformation and concerns. The Vaccine Information Statements provide an outline for discussing vaccine benefits and risk. Fact sheets, titled, Vaccines a safe choice and Helping Parents who question vaccines (available from the NIP website) may also be helpful.

Although a limited number of providers might choose to exclude from their practice those patients who question or refuse vaccination, the more effective public health strategy is to identify common ground and discuss measures that need to be followed if the patient's decision is to defer vaccination. Healthcare providers can reinforce key points regarding each vaccine, including safety, and emphasize risks encountered by unimmunized children. Parents should be advised of state laws pertaining to school or child care entry, which might require that unimmunized children stay home from school during outbreaks. Documentation of these discussions in the patient's record, including the refusal to receive certain vaccines (i.e., informed refusal), might reduce any potential liability if a vaccine-preventable disease occurs in the unimmunized patient.

Vaccine Safety Summary

- Many factors contribute to the need for an active and ongoing vaccine safety program
- Vaccines undergo extensive safety and efficacy evaluations prior to licensure
- Postlicensure evaluation is critical

Vaccine Safety Summary

- Provider's play an important role in helping to ensure vaccine safety
- Effective vaccine benefit-risk communication is important

CONCLUSION

Many factors contribute to the need for an active and ongoing vaccine safety program. Vaccines undergo extensive safety and efficacy evaluations in the laboratory, in animals, and in human clinical trials prior to licensure. Because rare reactions, delayed reactions, or reactions within sub-populations may not be detected before vaccines are licensed, postlicensure evaluation is critical. Providers also play and important role in helping to ensure vaccine safety and should discuss the benefits and risks of vaccination with parents, guardians, legal representatives, and adolescent and adult patients. More information about the topics discussed in this chapter can be obtained at http://www.cdc.gov/nip, and a list of vaccine safety resources has been included in Appendix F.

SELECTED REFERENCES

American Academy of Pediatrics. Pickering LK, ed. *Red Book:2003 report of the Committee on Infectious Diseases*. 26th ed. Elk Grove Village, IL: American Academy of Pediatrics;2003: pg 46-49.

Bohlke K, Davis RL, Marcy SM, Braun MM, Destefano F, Black SB, Mullooly JP, Thompson RS. Risk of Anaphylaxis after vaccination of children and adolescents. *Pediatrics*. 2003; vol.112 4:815-820

CDC. National Childhood Vaccine Injury Act: Requirements for permanent vaccination records and for reporting of selected events after vaccination. *MMWR* 1988;37:197-200.

CDC. Surveillance for safety after immunization. *MMWR* 2003;52 (no.SS-1).

CDC. Update: Vaccine side effects, adverse reactions, contraindications and precautions. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 1996;45(RR-12):1-35.

Chen RT and Hibbs B. Vaccine safety: Current and future challenges. *Ped Annals* 1998;27:445-64.

Chen RT, Glasser J, Rhodes P, et al. The Vaccine Safety Datalink (VSD) Project: A new tool for improving vaccine safety monitoring in the United States. *Pediatrics* 1997;99:765-73.

Chen RT, Rastogi SC, Mullen JR, et al. The Vaccine Adverse Event Reporting System (VAERS). *Vaccine* 1994;12:542-50.

Diphtheria is an acute, toxin-mediated disease caused by *Corynebacterium diphtheriae*. The name of the disease is derived from the Greek *diphthera*, meaning leather hide. The disease was described in the 5th Century B.C. by Hippocrates, and epidemics were described in the 6th Century A.D. 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 B.C.
- 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).

There are 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 which were not detected due to 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
  - Tonsillar and pharyngeal
  - Laryngeal
  - Cutaneous
  - Ocular
  - Genital

ANTERIOR NASAL DIPHTHERIA

The onset is indistinguishable from that of the common cold and is

Pharyngeal and Tonsillar Diphtheria

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

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 can be terminated rapidly by antitoxin and antibiotic therapy.

PHARYNGEAL AND TONSILLAR DIPHTHERIA

The most common sites of infection are the tonsils and the pharynx. 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 in color, or black if there has been bleeding. 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, 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 the only site involved. 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. In general, 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 vulvo-vaginal 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. Eye muscles, limbs, and diaphragm paralysis can occur after the fifth week. Secondary pneumonia and respiratory failure may result from diaphragmatic paralysis.

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

DEATH

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

LABORATORY DIAGNOSIS

Diagnosis is usually made based on the 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 the 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 which 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.

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

In the event that prior antibiotic therapy may have impeded a positive culture in a suspect diphtheria case, two sources of evidence may aid in presumptive diagnosis: (1) isolation of the *C. diphtheriae* from culturing of close contacts, and/or (2) a low non-protective diphtheria antibody titer in sera obtained prior to antitoxin administration (<0.1 I.U.) This is done by commercial laboratories and requires several days. To isolate *C. diphtheriae* from carriers, it is best to inoculate a Löffler's or Pai's 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

- **First used in 1891**
- **Produced in horses**
- **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 cases, 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 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 at all times through the CDC operator at (404) 639-2889. During office hours, 8:00 am - 4:30 pm EST, contact staff at the National Immunization Program, (404) 639-8255.

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 less 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 handled as 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).

TEMPORAL PATTERN

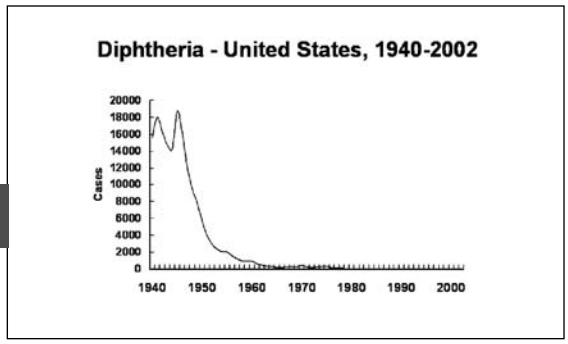
In temperate areas, diphtheria most frequently occurs during winter and spring.

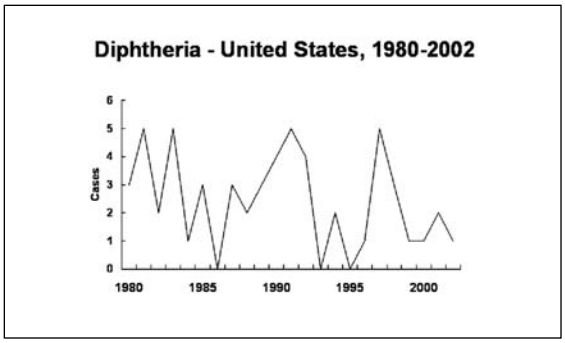
COMMUNICABILITY

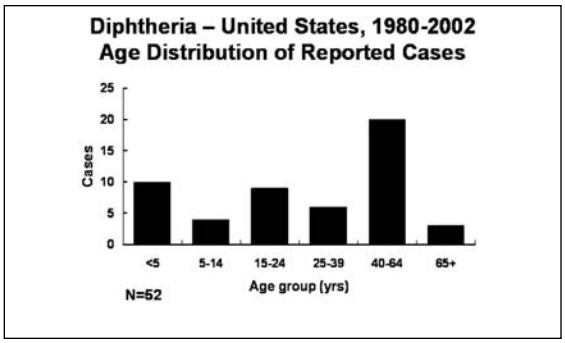
Transmission may occur as long as virulent bacilli are present in discharges and lesions. The time is variable, but organisms usually persist 2 weeks or less, and seldom more than 4 weeks, without antibiotics. Chronic carriers may shed organisms for 6 months or more. Effective antibiotic therapy promptly 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 <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 fell 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 non-toxigenic cutaneous isolates were excluded from reporting. Diphtheria was seen most frequently in Native Americans and persons in lower socioeconomic strata.

From 1980 through 2002, 54 cases of diphtheria were reported in the United States, an average of 2-3 per year (range, 0-5 cases per year). No cases were reported in 1993 and 1995. Only one case was reported each year in 1998, 1999, 2000, and 2002.

Of 52 reported cases with known age since 1980, 30 (58%) cases were in persons ≥20 years of age; 44% of cases were among persons ≥40 years of age. 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 American Indian community in South Dakota. Eight of these isolates were toxigenic. None of the infected persons had classic diphtheria disease, although 5 had either pharyngitis or tonsillitis. The presence of toxigenic *C. diphtheria* 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 5000 deaths were reported. In the six years from 1990 through 1995, the NIS accounted for more than 90 percent 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, is 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, then adsorbed onto an aluminum salt.

Single antigen diphtheria toxoid is not available. Diphtheria toxoid is available combined with tetanus as pediatric DT or adult Td, and with both tetanus toxoid and acellular pertussis vaccine as DTaP. 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. DTaP vaccines do not contain thimerosal as a preservative.

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 >0.1 international units 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 less 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 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 DT, DTP or DTaP is administered before the fourth birthday, a booster (fifth) dose is recommended at 4-6 years

DTaP, DT, and Td

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

Pertussis vaccine and pediatric DT used through age 6 years. Adult Td used for persons 7 years and older.

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, or Td

Routine DTaP Primary Vaccination Schedule

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

Children Who Receive DT

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

Routine DTaP Schedule
Children <7 years of age

Booster Doses

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

Routine Td Schedule
Unvaccinated Persons ≥7 Years of Age

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

Booster dose every 10 years

Diphtheria and Tetanus Toxoids
Adverse Reactions

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

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 individuals 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. If a dose is given sooner as part of wound management, the next booster is not needed for 10 years thereafter. More frequent boosters are not indicated and have been reported to result in an increased incidence and severity of local adverse reactions.

Td is the vaccine of choice for children 7 years and older, and for adults. A primary series is three or four doses, depending on whether the person has received prior doses of diphtheria-containing vaccine, and the age these doses were administered. The number of doses recommended for children who received one or more doses of DTP, DTaP, or DT before age 7 years is discussed above. For unvaccinated persons 7 years and older (including persons who cannot document prior vaccination), the primary series is three doses. The first two doses should be separated by at least 4 weeks, and the third dose given 6 to 12 months after the second. A booster dose of Td should be given every 10 years.

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 may not confer immunity. Individuals 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 uncommon.

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.

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** following a prior dose should not receive additional doses of diphtheria toxoid. Diphtheria toxoid should be deferred for those individuals who have **moderate to severe acute illness,** but persons with mild illness may be vaccinated. Immunosuppression and pregnancy are not contraindications to diphtheria toxoid.

Diphtheria and Tetanus Toxoids Contraindications and Precautions

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

VACCINE STORAGE AND HANDLING

The vaccine may be shipped without refrigeration if deliverable in 4 days. Refrigerant may be used. It should be refrigerated immediately upon arrival and stored at a temperature of 2°-8°C (35°-46°F). It should **not be frozen** — this reduces potency, and it should not be stored in direct contact with refrigerant.

SUSPECT CASE INVESTIGATION AND CONTROL

Immediate action on all highly suspect cases (including cutaneous) is warranted until shown not to be 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 epidemiological information (including vaccine history).

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

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 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 >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 <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 adequate course of antibiotic, and repeat cultures at a minimum of 2 weeks to assure 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.

SELECTED REFERENCES

CDC. Diphtheria, tetanus, and pertussis: Recommendations for vaccine use and other preventive measures. *MMWR* 1991;40(RR-10):1-28.

CDC. Pertussis vaccination: use of acellular pertussis vaccines among infants and young children. Recommendationd of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 1997;46(RR-7):1-25.

CDC. Update: Diphtheria Epidemic — Newly Independent States of the Former Soviet Union, January 1995-March 1996. *MMWR* 1996;45:693-7.

CDC. Toxigenic *Corynebacterium diphtheriae* — Northern Plains Indian community, August-October 1996. *MMWR* 1993;42:840-1, 847.

Chen RT, Broome CV, Weinstein RA, Weaver R, Tsai TF. Diphtheria in the United States, 1971-81. *Am J Public Health* 1985;75: 1393-7.

Farizo KM, Strebel PM, Chen RT, Kimbler A, Cleary TJ, Cochi SL. Fatal respiratory disease due to *Corynebacterium diphtheria:* case report and review of guidelines for management, investigation, and control. *Clin Infect Dis* 1993;16(1):59-68.

Hardy IRB. Diphtheria. In: Evans AS and Brachman PS, eds. *Bacterial Infections of Humans. Epidemiology and Control.* 3rd ed. New York, NY: Plenum Medical Book Company; 1998:253-68.

Orenstein WA, Hadler S, Wharton M. Trends in vaccine-preventable diseases. *Semin Pediatr Infect Dis* 1997;8:23-33.

Vitek CR and Wharton M. Diphtheria in the former Soviet Union: Reemergence of a pandemic disease. *Emerg Infect Dis* 1998;4:539-50.

Wharton M and Vitek CR. Diphtheria. In Plotkin SA, Orenstein WA, eds. *Vaccines*. 4th ed. Philadelphia, PA: Saunders, 2003:211-28.

Tetanus is an acute, often fatal, disease caused by an exotoxin produced by *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 B.C.) contain clinical descriptions of tetanus, it was Carle and Rattone who first produced tetanus in animals by injecting them with pus from a fatal human tetanus case in 1884. 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 during World War I. Tetanus toxoid was developed by Descombey in 1924, and the effectiveness of active immunization was demonstrated in World War II.

Tetanus

- First described by Hippocrates
- Etiology discovered in 1884 by Carle and Rattone
- Passive immunity 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 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 intestine 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.

Clostridium tetani

- Anaerobic gram-positive, spore-forming bacteria
- Spores found in soil, dust, animal feces; may persist for months to years
- Multiple toxins produced with growth of bacteria
- Tetanospasmin estimated human lethal dose = 2.5 ng/kg

Clostridium 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. Tetanospasmin is one of the most potent toxins known on a weight basis. 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 human.

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, brain, and 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

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.

Tetanus Clinical Features

- Incubation period 8 days (range, 3-21 days)
- Three clinical forms: Local (uncommon), 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

Neonatal Tetanus

- Generalized tetanus in newborn infant
- Infant born without protective passive immunity
- High fatality rate without therapy
- Estimated 215,000 deaths worldwide in 1998

Tetanus Complications

- Laryngospasm
- Fractures
- Hypertension
- Nosocomial infections
- Pulmonary embolism
- Aspiration
- Death

contraction and spasm. Seizures may occur, and the autonomic nervous system may also be affected.

CLINICAL FEATURES

The **incubation period** varies 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 a temperature rise of 2°-4°C above normal, sweating, elevated blood pressure, and episodic rapid heart rate. Spasms may occur frequently and last for several minutes. Spasms continue for 3-4 weeks. Complete recovery may take months.

Neonatal tetanus is a form of generalized tetanus that occurs in newborn infants. Neonatal tetanus occurs in infants born without protective passive immunity, because the mother is not immune. It usually occurs through infection of the unhealed umbilical stump, particularly when the stump is cut with an unsterile instrument. Neonatal tetanus is common in some developing countries (estimated >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, which 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 age ≥60 years (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.

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 maintanence 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 effect toxin bound to nerve endings. A single intramuscular dose of 3000 to 5000 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.

Due to 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). 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 or have an uncertain history of prior doses, need tetanus immune globulin (TIG) as well as Td toxoids. This is because early doses of toxoid do not induce immunity, but

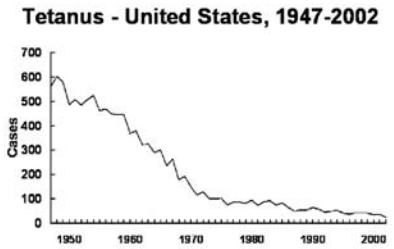
Tetanus Wound Management

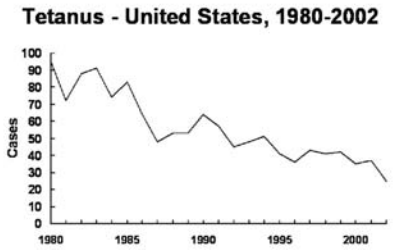
	Clean, minor wounds		All other wounds	
Vaccination History	Td	TIG	Td	TIG
Unknown or <3 doses	Yes	No	Yes	Yes
3+ doses	No*	No	No**	No

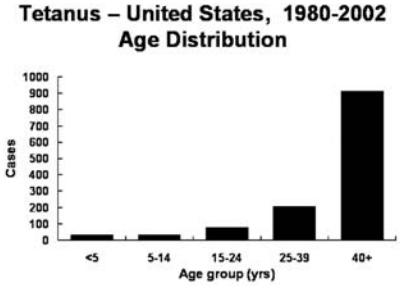
* Yes, if >10 years since last dose
** Yes, if >5 years since last dose

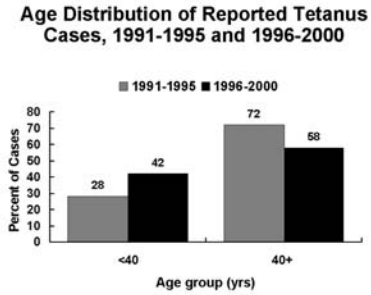
Tetanus Epidemiology

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









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

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

RESERVOIR

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

MODE OF TRANSMISSION

Transmission is primarily by contaminated wounds (apparent and inapparent). The wound may be major or minor. In recent years, however, a higher proportion of cases 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 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, there were 500-600 cases reported per year (approximately 0.4 cases per 100,000 population).

After the 1940s, reported tetanus incidence rates fell steadily. Since the mid-1970s, 50-100 cases have been reported annually (~ 0.05 cases per 100,000). The death-to-case ratio has declined from 30% to approximately 10% in recent years. An all-time low of 25 cases (0.01 cases per 100,000) were reported in 2002.

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 age <40 years. The age distribution of reported cases shifted to a younger age group in the last half of the 1990s. Persons <40 years increased from 28% of cases during 1991-1995 to 42% of cases during 1996-2000. This change in age distribution is a result of both an increase in cases in

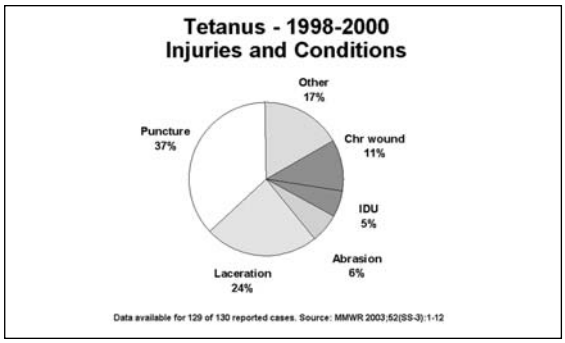
persons <40 years and a decrease in cases in older people. The increase in cases among younger persons is related in part to an increased number of cases among young injection drug users in California in the late 1990s.

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 2 cases reported since 1989. Neither of the infants' mothers had ever received tetanus toxoid.

During 1998-2000 (the most recent years 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 cases 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. Of these 18 patients, one (6%) death occurred; the death was in an injection-drug user (IDU) whose last dose of tetanus toxoid was 11 years before the onset of tetanus. A total of 110 patients reported <3 doses of tetanus toxoid or had an unknown vaccination history; 95 of these patients had an outcome reported. Nineteen deaths (20%) occurred among these 95 patients.

TETANUS TOXOID

CHARACTERISTICS

Tetanus toxoid was first produced in 1924. Tetanus toxoid immunizations were used extensively in the armed services during World War II. Tetanus cases among this population dropped 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 cases, 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 following the fluid toxoid.

DTaP, DT, and Td

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

Pertussis vaccine and pediatric DT used through age 6 years. Adult Td used for persons 7 years and older.

Tetanus toxoid is available as a single antigen preparation, combined with diphtheria as pediatric DT or adult Td, and with both diphtheria toxoid and acellular pertussis vaccine as DTaP. 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. There is virtually no reason to use single antigen tetanus toxoid. Tetanus toxoid should be given in combination with diphtheria toxoid, since periodic boosting is needed for both antigens.

IMMUNOGENICITY AND VACCINE EFFICACY

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, or Td

After a primary series of three properly spaced doses of tetanus toxoid in persons ≥7 years of age and four doses in children <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.

Following a properly administered primary series, almost all persons develop a protective level of antitoxin. Antitoxin levels decrease with time. While some persons may be protected for life, most persons have antitoxin levels that approach the minimal protective level by 10 years after the last dose. 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 in individuals who sustain a wound that is other than clean and minor, a booster is recommended for these persons 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.)

Routine DTaP Primary Vaccination Schedule

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

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 less 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.

Because of waning antitoxin titers, most individuals have antitoxin levels below the optimal level 10 years after the last dose of DTaP, DTP, DT, or Td. As a result, additional booster doses of tetanus and diphtheria toxoids (as Td) 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. If a dose is given sooner as part of wound management, the next booster is not needed for 10 years thereafter. More frequent boosters are not indicated and have been reported to result in an increased incidence and severity of local adverse reactions.

Td is the vaccine of choice for children 7 years and older, and for adults. A primary series is three or four doses, depending on whether the person has received prior doses of diphtheria-containing vaccine, and the age these doses were administered. The number of doses recommended for children who received one or more doses of DTP, DTaP, or DT before age 7 years is discussed above. For unvaccinated persons 7 years and older (including persons who cannot document prior vaccination), the primary series is three doses. The first two doses should be separated by at least 4 weeks, and the third dose given 6 to 12 months after the second.
A booster dose of Td should be given every 10 years.

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.

Children Who Receive DT

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

Routine DTaP Schedule
Children <7 years of age

Booster Doses

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

Routine Td Schedule
Unvaccinated Persons ≥7 Years of Age

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

Booster dose every 10 years

Diphtheria and Tetanus Toxoids
Adverse Reactions

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

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 (IOM) concluded that the available evidence favors a causal relationship between tetanus toxoid and both brachial neuritis and GBS, although these reactions are very rare.

Diphtheria and Tetanus Toxoids
Contraindications and Precautions

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

CONTRAINDICATIONS AND PRECAUTIONS TO VACCINATION

A **severe allergic reaction** (acute respiratory distress or collapse) following a prior dose of tetanus toxoid is a contraindication to receipt of tetanus toxoid. If a generalized reaction is suspected to represent allergy, it may be useful to refer an individual for appropriate skin testing before discontinuing tetanus toxoid immunization. A **moderate or severe acute illness** is reason to defer routine vaccination, but a minor illness is not.

If a contraindication to using tetanus toxoid-containing preparations exists, passive immunization with tetanus immune globulin (TIG) should be considered whenever an injury other than a clean minor wound is sustained.

VACCINE STORAGE AND HANDLING

DTaP, DT (pediatric), Td, DTP/Hib, and tetanus toxoid should be stored continuously at 2° - 8°C (35° - 46°F). The vaccine may be out of refrigeration for up to 4 days, but should be refrigerated immediately when received. Freezing reduces the potency of the tetanus component.

SELECTED REFERENCES

American Academy of Pediatrics. Tetanus. In Pickering L, ed. *Red Book 2003: Report of the Committee on Infectious Diseases*. 26th ed. Elk Grove Village, IL: American Academy of Pediatrics, 2003: 611-16.

CDC. Diphtheria, tetanus, and pertussis: Recommendations for vaccine use and other preventive measures: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 1991;40(RR-10):1-28.

CDC. Pertussis vaccination: use of acellular pertussis vaccines among infants and young children. Recommendationd of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 1997;46(RR-7):1-25.

CDC. Tetanus surveillance--United States, 1998-2000. *MMWR* 2003;52(SS-3):1-12.

Orenstein WA, Hadler S, Wharton M. Trends in vaccine-preventable diseases. *Semin Pediatr Infect Dis* 1997;8:23-33.

Sutter RW, Cochi SL, Sirotkin B, et al. Assessment of vital statistics and surveillance data for monitoring tetanus mortality, United States, 1979-1984. *Am J Epidemiol* 1990;131:132-42.

Sutter RW, Orenstein WA, Wassilak SGF. In: Evans AS and Brachman PS, eds. *Bacterial Infections of Humans: Epidemiology and Control*. 3rd ed. New York, NY: Plenum Medical Book Company, 1998:741-57.

Wassilak SGF, Roper MH, Murphy TV, Orenstein WA. Tetanus. In: Plotkin SA, Orenstein WA, eds. *Vaccines*. 4th ed. Philadelphia, PA: Saunders, 2003:745-81.

World Health Organization. The "high-risk" approach: the WHO-recommended strategy to accelerate elimination of neonatal tetanus. *Wlky Epidemiol Rec* 1996;71:33-36.

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. Prior to 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 98%, to an average of about 4,400 cases per year since 1980.

Pertussis remains a major health problem among children in developing countries, with an estimated 285,000 deaths resulting from the disease in 2001.

Pertussis

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

BORDETELLA PERTUSSIS

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

B. pertussis produces multiple antigenic and biologically active products, including pertussis toxin, filamentous hemagglutinin, agglutinogens, adenylate cyclase, pertactin, and tracheal cytotoxin. These products are responsible for the clinical features of pertussis disease, and an immune response to one or more produces immunity to subsequent clinical illness. Recent evidence suggests that immunity from *B. pertussis* infection may not 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 respiratory cilia, produce toxins that paralyze the cilia, and cause inflammation of the respiratory tract, thus interfering 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 work has shown the bacteria in alveolar macrophages.

Pertussis Pathogenesis

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

CLINICAL FEATURES

The **incubation period** of pertussis is commonly 7 to 10 days, with a range of 4 to 21 days, and rarely may be as long as 42 days. The clinical course of the illness is divided into three stages.

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.

Pertussis Clinical Features

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

Pertussis Clinical Features

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

Pertussis in Adults

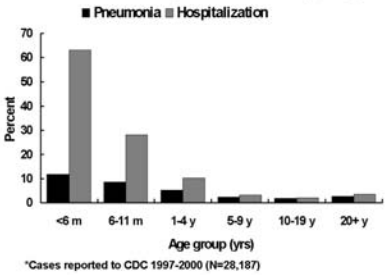
- Accounts for up to 7% of cough illnesses per year
- Disease often milder than in infants and children
- Adults often source of infection for children

Pertussis Complications*

Condition	Percent reported
Pneumonia	5.2
Seizures	0.8
Encephalopathy	0.1
Death	0.2
Hospitalization	20

*Cases reported to CDC 1997-2000 (N=28,187)

Pertussis Complications by Age



*Cases reported to CDC 1997-2000 (N=28,187)

It is during the **paroxysmal stage** that the diagnosis of pertussis is usually suspected. Characteristically, the patient has bursts, or paroxysms of numerous, rapid coughs, apparently due to difficulty expelling thick mucus from the tracheobronchial tree. At the end of the paroxysm, a long inspiratory effort is usually accompanied by a characteristic high-pitched whoop. During such an attack, the patient may become cyanotic (turn blue). Children and young infants, especially, appear very ill and distressed. Vomiting and exhaustion commonly follow the episode. The patient usually appears normal between attacks.

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

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

Older persons *(i.e.,* **adolescents and adults**), and those partially protected by the vaccine may become infected with *B. pertussis*, but usually have milder disease. Pertussis in these persons may present as a persistent (>7 days) cough, and may be indistinguishable from other upper respiratory infections. Inspiratory whoop is uncommon. *B. pertussis* is estimated to account for up to 7% of cough illnesses per year in older persons.

Even though the disease may be milder in older persons, these infected persons may transmit the disease to other susceptible persons, including unimmunized or underimmunized infants. Adults are often found to be the first case in a household with multiple pertussis cases.

COMPLICATIONS

Young infants are at highest risk for acquiring clinical pertussis, and for pertussis-associated complications. The most common complication, and the cause of most pertussis-related deaths, is secondary bacterial pneumonia. Data from 1997-2000 indicate that pneumonia occurred among 5.2% of all reported pertussis cases, and among 11.8% of infants <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. In 1997-2000, seizures and encephalopathy were reported among 0.8% and 0.1%, respectively, of all cases, and among 1.4%

and 0.2%, respectively, of infants <6 months of age.

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 1997-2000, 20% of all reported pertussis cases required hospitalization, including 63% of all infants <6 months of age. In this 4 year period, 62 deaths were due to pertussis (case-fatality rate 0.2%). Fifty-six (90%) of these deaths occurred in children <6 months of age.

LABORATORY DIAGNOSIS

The diagnosis of pertussis is usually based upon a characteristic history and physical examination. However, laboratory tests may be useful in young infants, atypical cases, and cases modified by vaccine.

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

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

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

Serological testing has proven useful in clinical studies, but is not yet standardized. Due to lack of association between antibody levels and immunity to pertussis, results of serologic testing are difficult to interpret. For these reasons, serologic testing is not widely available. In some areas it is used for clinical diagnosis and reporting, but in the absence of standardization, serologic test results should not be

relied upon for case confirmation for the purpose of national reporting. Cases meeting the clinical case definition that are serologically positive, but **not** culture positive or PCR positive, should be reported as probable cases.

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

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

MEDICAL MANAGEMENT

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

Erythromycin or trimethoprim-sulfamethoxazole prophylaxis should be administered for 14 days to all household and other close contacts of persons with pertussis, **regardless of age and vaccination status.** Although data from controlled clinical trials are lacking, prophylaxis of all household members and other close contacts may prevent or minimize transmission. All close contacts <7 years of age who have not completed the four-dose primary series should complete the series with the minimal intervals. Close contacts <7 years of age who have completed a primary series but have not received a dose of DTP or DTaP within 3 year's of exposure, should be given a booster dose.

EPIDEMIOLOGY

OCCURRENCE

Pertussis occurs worldwide.

Pertussis Epidemiology

- Reservoir — Human; Adolescents and adults
- Transmission — Respiratory droplets; Airborne rare
- Communicability — Maximum in catarrhal stage; Secondary attack rate up to 80%

RESERVOIR

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

TRANSMISSION

Transmission most commonly occurs by the respiratory route through contact with respiratory droplets, or by contact with airborne droplets of respiratory secretions. Transmission occurs less frequently by contact with freshly contaminated articles of an infected person. A silent carrier state is thought to exist, but is infrequent, transient in duration, and probably of little importance in maintain-

ing pertussis organisms in the community.

TEMPORAL PATTERN

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

COMMUNICABILITY

Pertussis is highly communicable, as evidenced by secondary attack rates of 80% among susceptible household contacts.

Persons with pertussis are most infectious during the catarrhal period and the first 2 weeks after cough onset (*i.e.*, approximately 21 days).

SECULAR TRENDS IN THE UNITED STATES

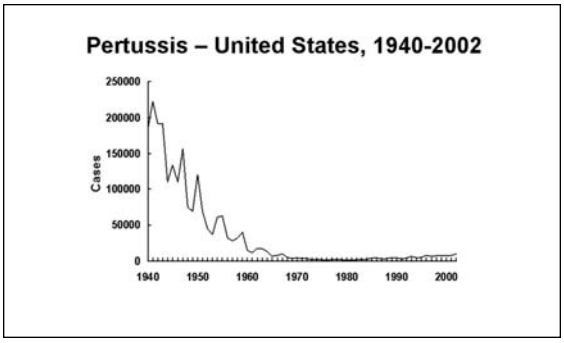
Prior to the availability of vaccine, pertussis was a common cause of morbidity and mortality among children. During the six years of 1940-1945, more than 1 million cases of pertussis were reported, an average of 175,000 cases per year (incidence of approximately 150 cases per 100,000 population).

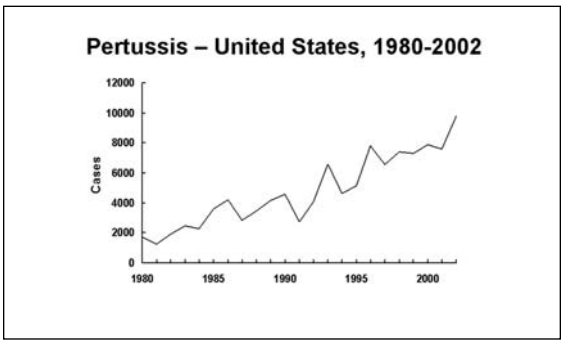
Following introduction of vaccine in the 1940s, pertussis incidence gradually fell, reaching 15,000 reported cases in 1960 (~8 per 100,000 population). By 1970, annual incidence was <5000 cases per year, and from 1980-1990, an average of 2,900 cases per year were reported (~1 per 100,000 population).

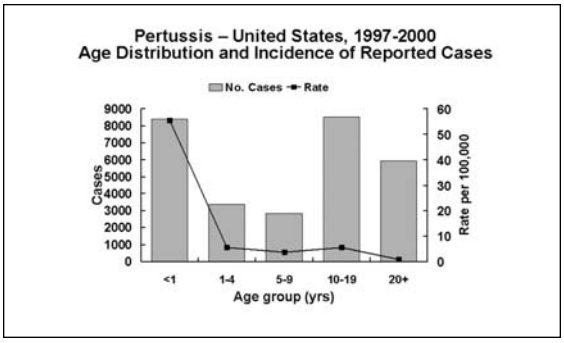
Pertussis incidence has been gradually increasing since the early 1980s. A total of 9,771 cases was reported in 2002, the largest number since 1964. The reasons for the increase are not clear, but may be a reflection of the 3-5 year cyclicity observed with the disease.

In 1997-2000, the highest annual pertussis incidence was among infants aged <1 year (55.5 cases per 100,000 population). In 2002, 24% of all reported cases were in this age group. Compared with surveillance data for 1994-1996, the pertussis incidence rate among adolescents and adults increased 62% and 60%, respectively, in 1997-2000. These increases could reflect a change in reporting or a true increase in incidence. In 1995, criteria for reporting a pertussis case changed in two ways: polymerase chain reaction (PCR) became a method of confirmation, and data collection began for pertussis cases epidemiologically linked to another pertussis case. These changes primarily affected the reporting among persons aged ≥10 years. Increased recognition and diagnosis of pertussis among older age groups probably contributed to the large recent 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.







CASE DEFINITION

The current case definition for pertussis was developed and adopted by the Council of State and Territorial Epidemiologists (CSTE) and the Centers for Disease Control and Prevention (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 post-tussive 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 Surveillance Manual (available on NIP website) for more information on case classification.

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

PERTUSSIS VACCINES

WHOLE-CELL PERTUSSIS VACCINE

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

Based on controlled efficacy trials conducted in the 1940s and on subsequent observational efficacy studies, a primary series of four doses of whole-cell DTP vaccine was 70% to 90% effective in preventing serious pertussis disease. Protection from pertussis vaccine decreased with time, resulting in little or no protection 5 to 10 years following the last dose. Local reactions such as redness, swelling, and pain at the injection site occurred following up to half of doses of whole-cell DTP vaccines. Fever, and other mild systemic events were also common. More severe systemic reactions, such as convulsions and hypotonic hyporesponsive episodes occurred less frequently (one case to 1,750 doses administered). Acute encephalopathy occurred even more rarely (0-10.5 cases per million doses administered). Experts disagreed on whether whole-cell pertussis vaccine caused lasting brain damage, but agreed that if the vaccine caused such damage it did so only rarely. Concerns about safety led to the development of more purified (acellular) pertussis vaccines that are associated with a lower frequency of adverse reactions.

Whole-Cell Pertussis Vaccine

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

ACELLULAR PERTUSSIS VACCINE

Acellular pertussis vaccines contain purified, inactivated components of *B. pertussis* cells. Several acellular pertussis vaccines have been developed that contain different components in varying concentrations. 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 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 3 antigens, mostly pertussis toxin (PT) and FHA. Tripedia (Aventis Pasteur) contains two components, FHA and PT, in equal amounts. Daptacel (Aventis Pasteur) contains four components, PT, FHA, pertacin, and fimbriae types 2 and 3.

IMMUNOGENICITY AND VACCINE EFFICACY

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.

VACCINATION SCHEDULE AND USE

Acellular pertussis vaccine (DTaP) is recommended for all doses of the pertussis schedule. Whole-cell vaccine (DTP) is no longer available in the U.S. The primary series of DTaP consists of four doses of vaccine, the first three doses given at 4-to 8-week intervals (minimum of 4 weeks), beginning at 6 weeks to 2 months of age. The fourth dose is given 6-12 months after the third to maintain adequate immunity for the ensuing preschool years. DTaP should be administered simultaneously with all other indicated vaccines.

The **fourth dose** of all brands of DTaP are licensed, and recommended by ACIP, to be administered at 15 to 18 months of age (17-20 months for Daptacel). However, ACIP recommends that in certain circumstances the fourth dose be given earlier than 15 months of age. ACIP recommends that the fourth dose of DTaP 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*

Acellular Pertussis Vaccine (DTaP)

- Purified "subunit" vaccines
- Intended to reduce adverse reactions
- Licensed for fourth and fifth doses in 1991
- Licensed for full series in 1996

Composition* of Acellular Pertussis Vaccines

Product	PT	FHA	PERT	FIM
Daptacel	10	5	3	5
Infanrix	25	25	8	--
Tripedia	23	23	--	--

*mcg per dose

DTaP Clinical Trials

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

Routine DTaP Primary Vaccination Schedule

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

DTaP Fourth Dose

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

*17-20 months for Daptacel

School Entry (fifth) Dose

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

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

Pertussis Vaccine in Adults

- No pertussis vaccine licensed for use in adults in the United States
- Acellular pertussis vaccine safe and immunogenic in adults
- Impact on disease or transmission unknown
- Not routinely recommended at this time

return for an additional visit at 15 to 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 4th birthday should receive a **fifth (booster) dose of DTaP** before entering school. This booster dose is not necessary if the fourth dose in the primary series was given on or after the 4th birthday. The booster dose increases protective antibody levels and may decrease the risk of school-age children transmitting the disease to younger siblings who are not fully vaccinated. Tripedia and Infanrix are approved for the fifth dose following a series of 4 doses of DTaP.

For children who have started the vaccination series with whole cell DTP, **DTaP should be substituted for any remaining doses of the pertussis series**. A pertussis vaccination series begun with whole cell DTP should be completed with DTaP.

ACIP recommends that the series be completed with the same brand of DTaP vaccine if possible. Limited data suggest that "mix and match" DTaP schedules do not adversely affect safety and immunogenicity. The vaccine provider might not know or have available the type of DTaP vaccine previously administered to a child. In this situation, any available DTaP vaccine should be used to continue or complete the vaccination series. Providers should not miss the opportunity to administer a dose of acellular pertussis vaccine for which the child is eligible if the vaccine used for the earlier doses is not available.

No pertussis-containing vaccine is currently licensed for **persons 7 years of age or older.** Vaccine reactions are thought to be more frequent in older age groups, and pertussis-associated morbidity and mortality decrease with increasing age. Vaccination with DTaP is not recommended after the 7th birthday. Studies are currently underway to determine if a booster dose of acellular pertussis vaccine administered to older children or adults may reduce the risk of infection with *B. pertussis*. This may in turn reduce the risk of transmission of *B. pertussis* to infants and young children who may be incompletely vaccinated.

No single antigen pertussis vaccine is available.

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.**

COMBINATION VACCINES CONTAINING DTaP

TRIHIBIT

One combination DTaP - Hib vaccine is available in the United States (TriHIBit, Aventis 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 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 aged ≥12 months, and has received at least one prior dose of Hib vaccine ≥2 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 3 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

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

*booster dose should follow prior dose by ≥2 months

PEDIARIX

In 2002, the U.S. Food and Drug Administration approved Pediarix (GlaxoSmithKline), the first pentavalent (5 component) combination vaccine licensed in the U.S. Pediarix contains DTaP (Infanrix), hepatitis B (Engerix-B), and inactivated polio vaccines. In the prelicensure studies, the proportion of children who developed a protective level of antibody, and the titer of antibody, was at least as high for 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 one, two, or three of the series, and the child is less than 7 years of age.

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

- May be used interchangeably with other pertussis-containing vaccines if necessary
- Can be given at 2, 4, and 6 months in infants who received a birth dose of hepatitis B vaccine (total of 4 doses)
- May be used in infants whose mothers are HBsAg positive or status unknown

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

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

OTHER DTaP ISSUES

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

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

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

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

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

Children who have recovered from documented pertussis do not need additional doses of pertussis vaccine. Satisfactory documentation includes recovery of *B. pertussis* on culture or typical symptoms and clinical course when epidemiologically linked to a culture-proven case, as may occur during outbreaks. When such confirmation of diagnosis is lacking, vaccination should be completed, because presumed pertussis syndrome may have been caused by

other *Bordetella* species, *Chlamydia trachomatis, Mycoplasma pneumoniae,* or certain viruses.
Pertussis accounts for a significant proportion of cough illnesses among adults. In addition, older children and adults with pertussis are often a source of infection for unimmunized or underimmunized children. However, no pertussis vaccine available in the United States is approved for use among persons aged 7 years or older. Studies have shown that acellular pertussis vaccine is safe and immunogenic among adults. However, it is not clear that administration of acellular pertussis vaccine to older children and adults will reduce the risk of their becoming infected with *B. pertussis*, or will reduce the risk of transmitting pertussis to young children. Administration of acellular pertussis vaccine to persons aged ≥7 years is not recommended. A pertussis vaccine for adults was recently approved in Canada, and may be available in the U.S. in the future.

ADVERSE REACTIONS FOLLOWING VACCINATION

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 3 doses. Local reactions appear to be more frequent after the 4th and/or 5th doses. **Mild systemic reactions** such as fever, drowsiness, fretfulness, and low grade fever may occur after either whole-cell DTP vaccination or DTaP vaccination. However, mild reactions following the first four doses are less common among children who receive DTaP. For instance, fever of >101° F is reported in 3%-5% of DTaP recipients compared with 16% of whole-cell DTP recipients. These reactions are self-limited and can be managed with symptomatic treatment with acetaminophen or ibuprofen. **Moderate or severe systemic events** (such as fever ≥105° F, febrile seizures, persistent crying lasting ≥3 hours, and hypotonic hyporesponsive episodes) have been reported rarely after administration of DTaP, and occur less frequently among children administered DTaP than among children administered whole-cell DTP. Rates of these less common reactions vary by symptom and vaccine, but generally occur in less than 1 in 10,000 doses. See the pertussis chapter in *Vaccines* textbook (2003) for a comprehensive review of DTaP adverse event data.

DTaP Adverse Reactions

- Local reactions
- Low grade fever
- More severe adverse reactions uncommon
- Local reactions more common following 4th and 5th doses

Information on adverse reactions following a full series of DTaP are 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 increased from 2% after the first dose of Tripedia to 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(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 different 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 is not known, but these conditions appear to be self-limited and resolve without sequelae.

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

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

CONTRAINDICATIONS AND PRECAUTIONS TO VACCINATION

DTaP Contraindications

- **Serious allergic reaction to vaccine component or following prior dose**
- **Encephalopathy occurring within 7 days after vaccination not due to another identifiable cause**

Contraindications to further vaccination with DTaP are **severe allergic reaction** to a vaccine component or following prior dose of vaccine, and **encephalopathy** not due to another identifiable cause within 7 days of vaccination.

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

DTaP Precautions (Warnings)*

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

*may consider use in outbreaks

Certain infrequent adverse reactions following pertussis vaccination will generally contraindicate subsequent doses of pertussis vaccine. These adverse reactions are **temperature of ≥40.5°C (105°F)** within 48 hours not due to another identifiable cause; **collapse or shock-like state** (hypotonic-hyporesponsive episode) within 48 hours; **persistent, inconsolable crying** lasting ≥3 hours, occurring within 48 hours; and **convulsions with or without fever** occurring within 3 days.

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

VACCINE STORAGE AND HANDLING

DTaP and DTP vaccines should be stored continuously at 2°-8°C (35°-46°F). The pertussis antigen is most susceptible to extremes of temperature, although normal ambient temperature up to 4 days will not destroy it. Exposure to freezing temperature substantially reduces the potency of the pertussis component.

PERTUSSIS SURVEILLANCE

Pertussis cases are reported to the Centers for Disease Control and Prevention 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 (SPSS). Although many pertussis cases are not reported, the surveillance system is useful for monitoring epidemiologic trends. For instance, the highest incidence of pertussis occurs in infancy, the age group at greatest risk for severe illness and complications. In recent years, the surveillance system has reflected an increase in the incidence of pertussis in all age groups, most notably among adolescents and adults.

Guidelines on pertussis surveillance and outbreak control are available on the National Immunization Program website at http://www.cdc.gov/nip/publications/pertussis/guide.htm.

SELECTED REFERENCES

American Academy of Pediatrics. Pertussis. In: Pickering LK ed. *Red Book: 2003 Report of the Committee on Infectious Diseases*. 26th ed. Elk Grove Village, IL: American Academy of Pediatrics, 2003:472-86.

Birkebaek NH, Kristiansen M, Seefeldt T, et al. *Bordatella pertussis* and chronic cough in adults. *Clin Infect Dis* 1999;29:1239-42.

CDC. Pertussis vaccination: Use of acellular pertussis vaccines among infants and young children. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 1997;46(RR-7):1-25.

CDC. Use of diphtheria toxoid-tetanus toxoid-acellular pertussis vaccine as a five-dose series. Supplemtal recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2000;49(RR-13):1-25.

CDC. Pertussis—United States, 1997-2000. *MMWR* 2002;51:73-76.

CDC. Pertussis outbreak among adults at an oil refinery—Illinois, August-October 2002. *MMWR* 2003;52:1-4.

Edwards K, Decker M. Pertussis Vaccine. In: Plotkin SA, Orenstein WA, eds. *Vaccines*. 4th edition. Philadelphia: Saunders; 2003:471-528.

Gangarosa EJ, Galazka AM, Phillips LM, et al. Impact of anti-vaccine movements on pertussis control: the untold story. *Lancet* 1998;351:356-61.

Guris D, Strebel PM, Bardenheir B, et al. The changing epidemiology of pertussis in the United States: increasing reported incidence in adolescents and adults, 1990-1996. *Clin Infect Dis* 1999;28:1230-7.

Woo EJ, Burwen DR, Gatumu, et al. Extensive limb swelling after immunization: Reports to the Vaccine Adverse Event Reporting System. *Clin Infect Dis* 2003;37:351-8.

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, paralysis.

Although records from antiquity mention crippling diseases compatible with poliomyelitis, it was Michael Underwood from England who, in 1789, first described a debility of the lower extremities in children that was recognizable as poliomyelitis. The first outbreaks in Europe were reported in the early 19th century, and outbreaks were reported in the United States a few years later. 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 increased age of 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. Polio incidence fell rapidly following introduction of effective vaccines. The last case of wild-virus polio acquired in the United States was in 1979, and global polio eradication may be achieved within the next decade.

Poliomyelitis

- First described by Michael Underwood in 1789
- First outbreak described in U.S. in 1843
- 21,000 paralytic cases reported in the United States in 1952
- Global eradication in near future

POLIOVIRUS

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

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

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

Poliovirus

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

PATHOGENESIS

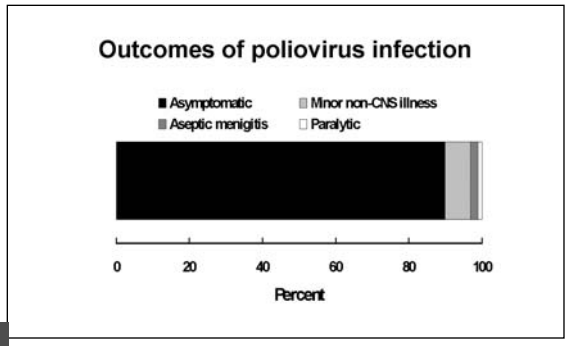
The virus enters through the mouth and primary multiplication of the virus occurs at the site of implantation in the pharynx and gastrointestinal tract. The virus is usually present in the throat and in the stool before the onset of illness. One week after onset there is little virus in the throat, but virus continues to be excreted in the stool for several weeks. The virus invades local lymphoid tissue, enters the blood stream, 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 from 3 to 35 days.



The response to poliovirus infection is highly variable and has been categorized based on 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.

Less 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 accounted for 79% of paralytic cases from 1969-1979. It is characterized by asymmetric paralysis that most often involves the legs. **Bulbar polio** accounted for 2% of cases and led to weakness of muscles innervated by cranial nerves. **Bulbospinal polio** accounted for 19% of cases and was a combination of bulbar and spinal paralysis.

The death-to-case ratio for paralytic polio is generally 2%-5% in

children and up to 15%-30% in 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" or "vaccine type."

SEROLOGY

Neutralizing antibodies appear early and may be at high levels by the time the patient is hospitalized and, therefore, a 4-fold rise may not be demonstrated.

CEREBROSPINAL FLUID (CSF)

The CSF in poliovirus infection usually contains an increased number of white blood cells (10 to 200 cells/mm^3, primarily lymphocytes) and a mildly elevated protein from 40 to 50 mg/100 ml.

EPIDEMIOLOGY

OCCURRENCE

At one time poliovirus infection occurred throughout the world. Transmission of wild poliovirus ceased 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 through the Western Hemisphere in 1991. The Global Polio Eradication Program has dramatically reduced poliovirus transmission throughout the world. Poliovirus transmission now occurs primarily in the Indian subcontinent, the Eastern Mediterranean, and Africa.

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.

Poliovirus Epidemiology

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

TEMPORAL PATTERN

Poliovirus infection typically peaks in the summer months in temperate climates. There is no seasonal pattern in tropical climates.

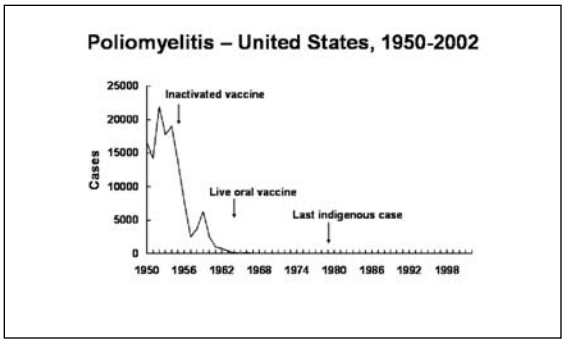
COMMUNICABILITY

Poliovirus is highly infectious, with seroconversion rates in susceptible household contacts of children nearly 100% and more than 90% in 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

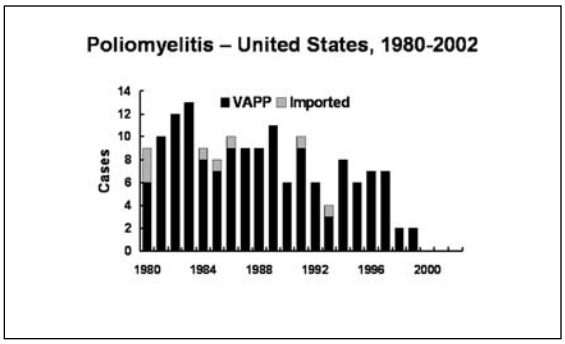
Before the 18th century, polioviruses probably circulated widely. Initial infections with at least one type probably occurred in early infancy, when transplacentally acquired maternal antibodies were high. Exposure throughout life probably provided continual boosting of immunity and paralytic infections were probably rare. (This view has been recently challenged based on data of lameness studies in developing countries.)

In the immediate prevaccine era, improved sanitation allowed less frequent exposure and increased the age of primary infection. There was infrequent boosting of immunity from natural exposure, accumulation of susceptibles, and ultimately the occurrence of epidemics, with 13,000 to 20,000 paralytic cases reported annually.



In the early vaccine era, the incidence dramatically decreased following IPV introduction in 1955. The decline continued following 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 these persons 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 was reported in 1999.

POLIOVIRUS VACCINES

Inactivated (Salk) 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 oral poliovirus vaccine (OPV) was licensed and largely replaced IPV use. OPV has been the vaccine of choice in the United States and most other countries of the world since 1963. An enhanced-potency IPV was licensed in November 1987, and first became available in 1988.

Poliovirus Vaccine

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

CHARACTERISTICS

INACTIVATED POLIOVIRUS VACCINE (IPV)

Two enhanced forms of inactivated poliovirus vaccine are currently licensed in the United States, but only one vaccine (IPOL, Aventis 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, and trace amounts of neomycin, streptomycin, and polymyxin B. It is supplied in a single dose prefilled syringe, and should be administered by either subcutaneous or intramuscular injection.

Inactivated Polio Vaccine

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

ORAL POLIOVIRUS VACCINE (OPV)

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 (Vero) kidney cell culture. The vaccine is supplied as a single 0.5 ml dose in a plastic dispenser. The vaccine contains trace amounts of streptomycin and neomycin. 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 six weeks after a dose. Maximum viral shedding occurs in the first 1-2 weeks after vaccination.

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.

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

IMMUNOGENICITY AND VACCINE EFFICACY

IPV

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 2 doses, and at least 99% are immune following 3 doses. Protection against paralytic disease correlates with the presence of antibody.

Inactivated Polio Vaccine

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

Oral Polio Vaccine

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

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 to contacts of OPV recipients

IPV appears to produce less local gastrointestinal immunity than does OPV, so persons who receive IPV are more readily infected with wild polio virus than OPV recipients. A person who received IPV could become infected with wild poliovirus in an endemic area and could be shedding wild virus upon return to the United States. The infected person would be protected from paralytic polio, but the wild virus being shed in the stool could spread and result in transmission to a contact.

The duration of immunity to IPV is not known with certainty, although it probably provides protection for many years after a complete series.

OPV

OPV is highly effective in producing immunity to poliovirus. A single dose of OPV produces immunity to all three vaccine viruses in about 50% of recipients. Three doses produce immunity to all 3 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 oral polio vaccine 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 vaccine-associated paralytic polio (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.

ACIP recommended an increase in use of IPV through a sequential schedule of IPV followed by OPV in 1996. This recommendation was intended to *reduce* the occurrence of vaccine-associated 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, there would continue to be a risk of VAPP 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. In order 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 manufactured or routinely available in the United States. Exclusive use of inactivated polio vaccine eliminated the shedding of live vaccine virus, and eliminated any risk of vaccine associated poliomyelitis.

A primary series of inactivated polio vaccine 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 to 18 months of age. The first and second doses of IPV are necessary to induce a primary immune response, and the third dose of IPV ensures "boosting" of antibody titers to high levels. The preferred interval between the second and third doses of IPV is 2-8 months. However, if accelerated protection is needed, the minimum interval between doses of IPV is 4 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. It is not necessary to repeat or add doses if the interval between doses is prolonged.

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.

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 one, two, or three of the series, and the child is less than 7 years of age. Pediarix is not approved for fourth dose of the IPV series, or the fourth or fifth doses of the DTaP series.

Polio Vaccination Recommendations

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

Polio Vaccination Schedule

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

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 constitutes a complete 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

Polio Vaccination of Adults

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

Polio Vaccination of Unvaccinated Adults

- IPV
- Use standard IPV schedule if possible (0, 1-2 months, 6-12 months)
- May separate doses by 4 weeks if accelerated schedule needed

Polio Vaccination of Previously Vaccinated Adults

- Previously complete series
  - –administer one dose of IPV
- Incomplete series
  - –administer remaining doses in series
  - –no need to restart series

POLIO VACCINATION OF ADULTS

Routine vaccination of adults (≥18 years of age) who reside in the United States is not necessary or recommended because most adults are already immune and have a very small risk of exposure to wild poliovirus in the United States.

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

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

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

In some circumstances time will not allow completion of this schedule. If 8 weeks or more are available before protection is needed, three doses of IPV should be given at least 4 weeks apart. If 4-8 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 doses and who are at increased risk of exposure to poliomyelitis should be given one dose of IPV. The need for further supplementary doses has not been established. Only one supplemental dose of polio vaccine is recommended for adults who have received a complete series (*i.e.* it is not necessary to administer additional doses for subsequent travel to a polio endemic country).

Adults who have previously received less than a full primary course of OPV or IPV and who are at increased risk of exposure to poliomyelitis should be given the remaining doses of IPV, regardless of the interval since the last dose and type of vaccine previously received. It is not necessary to restart the series of either vaccine if the schedule has been interrupted.

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 among persons sensitive to these antibiotics.

Polio Vaccine Adverse Reactions

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

VACCINE-ASSOCIATED PARALYTIC POLIOMYELITIS (VAPP)

Vaccine-associated paralytic polio (VAPP) is a rare adverse reaction following live oral poliovirus vaccine. Inactivated poliovirus vaccine does not contain live virus, so it cannot cause VAPP. The mechanism of VAPP is believed to be a mutation, or reversion, of the vaccine virus to a more neurotropic form. These mutated viruses are called revertants. Reversion is believed to occur in almost all vaccine recipients, but it only rarely results in paralytic disease. The paralysis that results is identical to that caused by wild virus, and may be permanent.

Vaccine-Associated Paralytic Polio

- Increased risk in persons >18 years
- Increased risk in persons with immunodeficiency
- No procedure available for identifying persons at risk of paralytic disease
- Usually permanent

VAPP is more likely to occur in persons ≥18 years of age than in children, and is much more likely to occur in immunodeficient children than in those who are immunologically normal. Compared with immunocompetent children, the risk of VAPP is almost 7000 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 persons with paralytic polio were reported in the United States; 144 (95%) of these cases were VAPP, and the remaining 8 persons acquired documented or presumed wild virus polio outside the U.S. Of the 144 VAPP cases reported during 1980-1998, 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 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.

Vaccine-Associated Paralytic Polio (VAPP) 1980-1998

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

The risk of VAPP was 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 1 case per 2.4 million doses. Forty-nine paralytic cases were reported among immunologically normal recipients of OPV from 1980 through 1994. 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. The risk of VAPP was 1 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 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 in the United States was reported in 1999.

CONTRAINDICATIONS AND PRECAUTIONS TO VACCINATION

Polio Vaccine
Contraindications and Precautions

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

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 individuals 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).

STORAGE AND HANDLING

IPV may be shipped without refrigeration provided it is delivered within 4 days. It should be maintained at 2°-8°C (35°-46°F). 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 epidemiological information (including vaccine history and contact with OPV vaccines) on any suspected case of paralytic polio. Notify the National Immunization Program, Centers for Disease Control and Prevention ([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 isolates and serology.

Even one case of paralytic poliomyelitis demands immediate attention. If the evidence indicates vaccine-associated disease, then no outbreak control program is needed. If, however, evidence indicates wild virus (for example, two cases in a community), then all unvaccinated individuals 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 >20,000 cases in 1952 to <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 (NIDs), 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.

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 $240 million to support the eradication initiative.

POSTPOLIO SYNDROME

After an interval of 30-40 years, 25%-40% of people 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 enhance 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 gender. The pathogenesis of postpolio syndrome

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 by 2005

Wild Poliovirus 1988

Wild Poliovirus 2002

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.

Several support groups have been established to assist and provide information to persons with postpolio syndrome, and their families.

International Polio Network
5100 Oakland Avenue, #206
St. Louis, MO 63110-1406
(314) 534-0475

March of Dimes
Birth Defects Foundation
Community Services Dept
1275 Mamaroneck Ave.
White Plains, NY 10605
(914) 428-7100

SELECTED REFERENCES

CDC. Progress toward global eradication of poliomyelitis eradication, 2002. *MMWR* 2003;52:366-9.

CDC. Poliomyelitis prevention in the United States: Updated recommendations of the Advisory Committee on Immunization Practices. (ACIP). *MMWR* 2000;49(RR-5):1-22.

CDC. Apparent global interruption of wild poliovirus type 2 transmission. *MMWR* 2001;50:222-4.

CDC. Certification of poliomyelitis eradication--the Americas, 1994. *MMWR* 1994;43:720-2.

Strebel PM, Sutter RW, Cochi SL, et al. Epidemiology of poliomyelitis in the United States: one decade after the last reported case of indigenous wild virus-associated disease. *Clin Infect Dis* 1992;14:568-79.

Sutter RW, Brink EW, Cochi SL, et al. A new epidemiologic and laboratory classification system for paralytic poliomyelitis cases. *Am J Public Health* 1989;79:495-8.

Haemophilus influenzae was first described by Pfeiffer in 1892. During a major outbreak of influenza, he found the bacteria in the sputum of patients, and proposed a causal association between this species 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 showed 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 <5 years of age. Almost all serious Hib infections were among children <5 years of age; approximately one in 200 children developed invasive Hib disease before the age of 5 years. Two-thirds of cases were among children <18 months of age.

***Haemophilus influenzae* type b**

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

HAEMOPHILUS INFLUENZAE

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

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

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

Haemophilus influenzae

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

PATHOGENESIS

The organism enters the body through the nasopharynx. Organisms colonize the nasopharynx and may remain only transiently or for several months in the absence of symptoms ("asymptomatic carrier"). In the prevaccine era, Hib could be isolated from the nasopharynx of 0.5%-3% of normal infants and children, uncommonly in adults. Nontypable (unencapsulated) strains are also frequent inhabitants of the human respiratory tract and are generally non-invasive.

In some persons the organism causes an invasive infection. The exact mode of invasion to the blood stream is unknown. Antecedent viral or mycoplasma infection of the upper respiratory tract may be a contributing factor. The bacteria spread in the bloodstream to dis-

***Haemophilus influenzae* type b**
Pathogenesis

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

tant sites in the body. Meninges are especially likely to be affected.

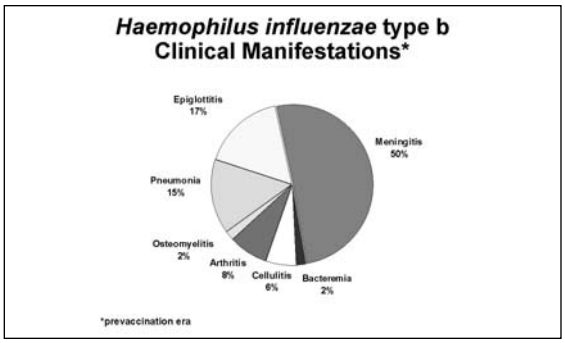
The most striking feature of Hib disease is **age-dependent susceptibility**. Passive protection of some infants is provided by transplacentally acquired maternal IgG antibodies and breastfeeding during the first 6 months of life. Peak attack rates occur at 6-7 months of age, declining thereafter. Hib disease is uncommon beyond 5 years of age. 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 post-vaccination correlated with protection in studies following vaccination with unconjugated 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 "natural" 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.



Haemophilus influenzae type b
Meningitis

- Accounted for approximately 50%-65% of cases
- Hearing impairment or neurologic sequelae in 15%-30%
- Case fatality rate 2%-5% in spite of effective antimicrobial therapy

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. The mortality rate is 2%-5%, despite appropriate antimicrobial therapy. Neurologic sequelae occur in 15%-30% of survivors.

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 nontypable strains. Hib strains account for only 5%-10% of *H. influenzae* causing otitis media.

LABORATORY DIAGNOSIS

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

All isolates of *Haemophilus influenzae* should be serotyped. This is an extremely important laboratory procedure that should be performed on every isolate of *Haemophilus influenzae*, especially those obtained from children <15 years of age. This test determines whether an isolate is type b, and is important because only type b 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 the diagnosis of patients who have been partially treated with antimicrobials and the organism may not be viable on culture. Two types 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 (CIE)** is similar to latex agglutination, but is less sensitive, takes longer, and is more difficult to perform.

MEDICAL MANAGEMENT

Hospitalization is generally required. Antimicrobial therapy with an effective third-generation cephalosporin (cefotaxime or ceftriaxone), or chloramphenicol in combination with ampicillin, should be begun immediately. 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

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

Haemophilus influenzae type b Epidemiology

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

EPIDEMIOLOGY

OCCURRENCE

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

RESERVOIR

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

TRANSMISSION

Primary mode is presumably by respiratory droplet spread, although firm evidence for this mechanism is lacking.

TEMPORAL PATTERN

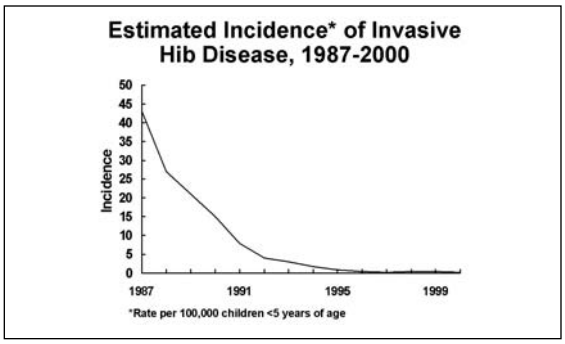
Several studies in the prevaccine era described a bimodal seasonal pattern in the United States, with one peak between September and December, and a second peak between March and May. The reason for this bimodal pattern is not known.

COMMUNICABILITY

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

SECULAR TRENDS IN THE UNITED STATES

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



Prior to the availability of national reporting data, several areas carried out 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 fall dramatically in the late 1980s, coincident with licensure of conjugate Hib vaccines, and has declined by >99% compared to the prevaccine era.

From 1996 through 2000, an average of 1,247 invasive *Haemophilus influenzae* cases 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 <5 years of age. Serotype was know for 76% of the invasive cases among children age <5 years. 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, therefore 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 in children 6-11 months of age. Children 60 months of age and older account for <10% of invasive disease.

In 1998-2000, approximately 44% of children less than 5 years of age with confirmed invasive Hib disease were less 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 (<3 doses) or their vaccination status was unknown. Thirty-two percent of children aged 6-59 months with confirmed type b disease had received 3 or more doses of Hib vaccine, including 22 who had received a booster dose 14 or more days prior to onset of their illness. The cause of Hib vaccine failure in these children is not known.

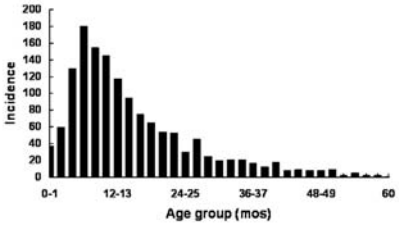
Risk factors for Hib disease include host factors and exposure factors that increase the likelihood of exposure to Hib. Exposure factors include household crowding, large household size, day-care attendance, low socioeconomic status, low parental education levels, and school-aged siblings. Host factors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

Protective factors (effect limited to <6 months of age) include breast-feeding and passively acquired maternal antibody.

Secondary Hib disease is defined as illness within 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 disease 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 and 2 years of age and younger to 0% among contacts the age of 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 case, 20% during the second week, and 16% during the third and fourth weeks.

There are conflicting data regarding the risk of secondary transmission among **day-care contacts**. Secondary attack rates have varied from 0% to as high as 2.7%. Most studies seem to suggest that day-care contacts are at relatively low risk for secondary transmission of Hib disease.

***Haemophilus influenzae* type b, 1986**
Incidence* by age group



*Rate per 100,000 population

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

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

***Haemophilus influenzae* type b**
Risk factors for invasive disease

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

Haemophilus influenzae type b Polysaccharide Vaccine

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

Polysaccharide Vaccines

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

Polysaccharide Conjugate Vaccines

- Stimulates T-dependent immunity
- Enhanced antibody production, especially in young children
- Repeat doses elicit booster response
- Antibody is biologically active in vitro

Haemophilus influenzae type b Conjugate Vaccines

- Pure polysaccharide vaccines (1985-1989) not effective in infants
- 3 conjugate vaccines licensed for use in infants
- Chemically and immunologically different

HAEMOPHILUS INFLUENZAE TYPE B VACCINE

CHARACTERISTICS

A pure polysaccharide vaccine (HbPV) was licensed in the United States in 1985. The vaccine was not effective among 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 response, and poor immunogenicity in children <2 years of age. In addition, no boost in antibody titer was observed with repeated doses, the antibody which was produced was relatively low-affinity IgM, and switching to IgG production was poor.

HAEMOPHILUS INFLUENZAE TYPE B *POLYSACCHARIDE-PROTEIN CONJUGATE VACCINES*

Conjugation is the process of chemically bonding a polysaccharide (a poor 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 <18 months of age. PRP-D is no longer available in the U.S.

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

Haemophilus influenzae type b Conjugate Vaccines

Vaccine	Protein Carrier	Manufacturer
HbOC (HibTITER)	Mutant diphtheria protein	Wyeth
PRP-T (ActHIB)	Tetanus toxoid	Aventis Pasteur
PRP-OMP (PedvaxHIB)	Meningococcal group B outer membrane protein	Merck & Co. Inc.

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 2 or 3 doses. Clinical efficacy has been estimated at 95% to 100%. Invasive Hib disease in a completely vaccinated infant is very rare.

Hib vaccine is immunogenic in patients with increased risk for invasive disease, such as those with sickle-cell disease, leukemia, human immunodeficiency virus (HIV) infection, and in those who have had splenectomies. 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

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

which vaccine is used for the primary series.

The optimal interval between doses is 2 months, with a **minimum interval** of 4 weeks. At least 8 weeks should separate the booster dose from the previous (2nd or 3rd) 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 3 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

***Haemophilus influenzae* type b Vaccine**

- Vaccination at <6 weeks of age may induce immunologic tolerance to Hib antigen
- Minimum age 6 weeks
- Minimum interval 1 month

***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

booster dose regardless of what was received in the primary series.

Unvaccinated children 7 months of age and older may not require a full series of 3 or 4 doses. The number of doses a child needs to complete the series depends on the child's current age.

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

Vaccine	Age at 1st Dose (Months)	Primary Series	Booster
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, 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, 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 (that is, 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 3 or 4 dose series.

The ACIP does not address the issue of vaccination of children with a lapsed Hib series. However, the 2000 American Academy of Pediatrics *Red Book* does provide some guidance. Information from the 2000 *Red Book* is summarized in the following table.

Hib Vaccination Schedule for Children with Lapsed Series (from AAP Red Book, 25th Edition, 2000)

Current Age (Months)	Prior Vaccination History	Recommended Regimen
7-11	1 dose	1 dose at 7-11 mos, booster at least 2 mos later at 12-15 mos
7-11	2 doses of HbOC or PRP-T	Same as above
12-14	2 doses before 12 mos	1 dose of any licensed conjugate
12-14	1 dose before 12 mos	2 doses of any licensed conjugate separated by 2 mos
15-59	Any incomplete schedule	1 dose of any licensed conjugate

Hib invasive disease does not always result in development of protective anti-PRP antibody levels. **Children <24 months of age who develop invasive Hib disease** should be considered unimmunized and 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
Vaccination following invasive disease

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

VACCINATION OF OLDER CHILDREN AND ADULTS

In general, **children >59 months of age** do not need Hib vaccination. The majority of these 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. These high-risk persons 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, and infection with human immunodeficiency virus. Previously unvaccinated persons >59 months of age with one of these high-risk conditions should be given at least one pediatric dose of any Hib conjugate vaccine.

Haemophilus influenzae type b Vaccine
Use in older children and adults

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

COMBINATION VACCINES

Two combination vaccines that contain *Haemophilus influenzae* type b are available in the United States - a DTaP-Hib combination (TriHIBit, Aventis Pasteur), and a hepatitis B - Hib combination (COMVAX, Merck Vaccine Division). Combination vaccines containing whole-cell pertussis vaccine and Hib are no longer available in the United States.

Combination Vaccines Containing Hib

- DTaP – Hib
  –TriHIBit
- Hepatitis B – Hib
  – COMVAX

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

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

TriHIBit

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

*booster dose should follow prior dose by ≥2 months

COMVAX

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

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 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 aged ≥12 months, **and** has received at least one prior dose of Hib vaccine ≥2 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 3 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.

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 micrograms (pediatric dose) of Merck's hepatitis B vaccine. COMVAX is licensed for use when either or both antigens are indicated. However, Hib vaccine should not be given to infants <6 weeks of age because of the potential of immune tolerance to the Hib antigen.

COMVAX should not be used in infants <6 weeks of age *(i.e.*, the birth dose of hepatitis B, or a dose at one month of age, if the infant is on a 0-1-6 schedule). COMVAX is not licensed for infants whose mothers are known to be hepatitis B surface antigen positive *(i.e.*, acute or chronic infection with hepatitis B virus). However, the vaccine contains the same dose of Merck's hepatitis B vaccine recommended for these infants, so response to the hepatitis B component of COMVAX should be adequate. 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.

ADVERSE REACTIONS FOLLOWING VACCINATION

Adverse reaction following Hib conjugate vaccines are not common. Swelling, redness, and/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. Available information on adverse reaction suggests that the risks for local and systemic reactions following TriHIBit administration are similar to those following concurrent administration of its individual component vaccines, and are probably due to the DTaP vaccine.

All serious adverse events that occur after receipt of any vaccine should be reported to the Vaccine Adverse Events Reporting System (VAERS).

Haemophilus influenzae type b Vaccine
Adverse Reactions

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

CONTRAINDICATIONS AND PRECAUTIONS TO VACCINATION

Vaccination with Hib conjugate vaccine is contraindicated in persons known to have experienced anaphylaxis following a prior dose of that vaccine. Vaccination should be delayed in 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 among children <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).

Haemophilus influenzae type b Vaccine
Contraindications and Precautions

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

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 (2°-8°C [35°-46°F]). Hib vaccine must not be frozen. Hib vaccines are stable for 30 days after reconstitution if the vaccine is stored at refrigerator temperature.

Opened multidose vials may be used until the expiration date printed on the package if they are not contaminated. ActHIB and TriHIBit should be used within 24 hours of reconstitution.

SURVEILLANCE AND REPORTING OF HIB DISEASE

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

RIFAMPIN PROPHYLAXIS

Several studies have shown that rifampin eradicated Hib carriage in ≥95% of contacts of primary Hib cases, including children in day-care facilities.

Contacts who develop symptoms suggestive of invasive Hib disease, such as fever or headache, should be evaluated promptly.

Rifampin chemoprophylaxis for **household contacts** is no longer indicated if all contacts aged <4 years are fully vaccinated against Hib disease. A child is considered fully immunized against Hib disease following (a) at least one dose of conjugate vaccine at 15 months of age; (b) two doses of conjugate vaccine at 12-14 months of age; or (c) two or more doses of conjugate vaccine at <12 months of age, followed by a booster dose at 12 months of age. In households with one or more infants <12 months of age (regardless of vaccination status) or with a child aged 1-3 years who is inadequately vaccinated, all household contacts should receive rifampin prophylaxis following a case of invasive Hib disease that occurs in any family member. The recommended dose is 20 mg/kg as a single daily dose (maximal daily dose 600 mg) for 4 days. Neonates (<1 month of age) should receive 10 mg/kg once daily for 4 days.

The use of rifampin in **daycare classrooms** is controversial. If a case of Hib disease has occurred, and any children less than 2 years of age have been exposed, all parents should be notified. Although data on risk are not optimal, all students (regardless of age) and staff in the classroom should receive rifampin prophylaxis according to the above regimen. However, rifampin prophylaxis is not necessary if all children <4 years of age are fully immunized.

Rifampin is contraindicated in pregnant women, as its effect on the fetus has not been established and it is teratogenic in laboratory animals.

Rifampin prophylaxis should be instituted as rapidly as possible. If more than 14 days have passed since the last contact with the index case, the benefit of rifampin prophylaxis is likely to be decreased.

The index case should be treated with the same rifampin regimen before discharge from the hospital, since antimicrobials used to treat invasive disease do not reliably eradicate carriage.

Children in day-care classrooms who are to receive chemoprophylaxisand who have received the Hib vaccine should also receive rifampin. However, if all children <4 years of age are fully immunized, chemoprophylaxis is not necessary.

Side effects may occur in up to 20% of recipients, and include nausea, vomiting, diarrhea, headache, and dizziness. Rifampin usually causes orange discoloration of urine. It may also cause discoloration of soft contact lenses and lens implants, or ineffectiveness of oral contraceptives.

SELECTED REFERENCES

American Academy of Pediatrics. *Haemophilus influenzae* infections. In: Pickering L ed. *Red Book: 2003 Report of the Committee on Infectious Diseases*. 26th ed. Elk Grove Village, IL: American Academy of Pediatrics, 2003:293-301.

Bisgard KM, Kao A, Leake J, et al. *Haemophilus influenzae* invasive disease in the United States, 1994-1995: Near disappearance of a vaccine-preventable childhood disease. *Emerg Infect Dis* 1998;4:229-37.

CDC. *Haemophilus* b conjugate vaccines for prevention of *Haemophilus influenzae* type b disease among infants and children two months of age and older. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 1991;40(RR-1):1-7.

CDC. Progress toward elimination of *Haemophilus influenzae* type b disease among infants and children — United States, 1998-2000. *MMWR* 2002;51:234-37.

CDC. *Haemophilus influenzae* invasive disease among children aged <5 years - California, 1990-1996. *MMWR* 1998;47:737-40.

Decker MD and Edwards KM. *Haemophilus influenzae* type b vaccines: history, choice and comparisons. *Pediatr Infect Dis J* 1998;17:S113-16.

Kostman JR, Sherry BL, Fligner CL, et al. Invasive *Haemophilus influenzae* infections in older children and adults in Seattle. *Clin Infect Dis* 1993;17(3):389-96.

Murphy TV, Pastor P, Medley F, Osterholm MT, Granoff DM. Decreased Haemophilus colonization in children vaccinated with *Haemophilus influenzae* type b conjugate vaccine. *J Pediatr* 1993;122:517-23.

Orenstein WA, Hadler S, Wharton M. Trends in vaccine-preventable diseases. *Semin Pediatr Infect Dis* 1997;8:23-33.

Measles is an acute viral infectious disease. There are references to measles as early as the 7th century. The disease was described by Rhazes in the 10th century as "more dreaded than smallpox."

In 1846, Peter Panum described the incubation period of measles and lifelong immunity. 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 U.S. in 1963 (Edmonston B strain).

Before a vaccine was available, infection with measles virus was nearly universal during childhood with more than 90% of persons immune by age 15 years. Measles is a common and often fatal disease in developing countries. The world Health Organization estimates there were 30-40 million cases and 745,000 deaths from measles in 2001.

Measles

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

MEASLES VIRUS

The measles virus is a paramyxovirus, genus Morbillivirus. It is 100 to 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 (<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, there is a second viremia, which occurs 5 to 7 days after initial infection. During this viremia, there may be infection of the respiratory tract and other organs. Measles virus is shed from the nasopharynx beginning with the prodrome until 3-4 days after rash onset.

Measles Pathogenesis

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

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).

Measles Clinical Features

- Incubation period 10-12 days

Prodrome

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

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), and/or conjunctivitis.

Koplik's 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.

Measles Clinical Features

Rash

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

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

Measles Complications

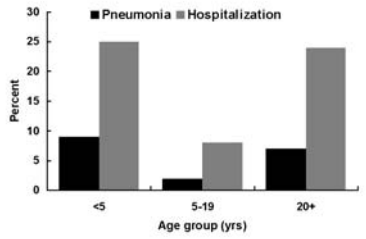
Condition	Percent reported
Diarrhea	8
Otitis media	7
Pneumonia	6
Encephalitis	0.1
Death	0.2
Hospitalization	18

Based on 1985-1992 surveillance data

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

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

Measles Complications by Age Group



Acute **encephalitis** is reported 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. Case fatality rate is approximately 15%. Some form of residual neurologic damage occurs in as many as 25%. **Seizures** (with or without fever) are reported in 0.6% to 0.7% of reported cases.

Death from measles has been reported in approximately 1-2 per 1,000 reported cases in the United States in recent years. 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 degenera-

tive central nervous system disease believed to be due to persistent measles virus infection of the brain. Average onset occurs 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-birth-weight 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 U.S. from 1963 to 1967. KMV sensitized 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 post-exposure 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 Immune Deficiency 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 <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., nasopharynx, urine)
- 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 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 of rash onset, and should not be collected more than 10 days after rash onset. A detailed protocol for collection of specimens for viral isolation is available from the CDC.

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 tests for IgM antibody require only a single serum specimen and are diagnostic if positive. The preferred reference test is a capture IgM test developed by CDC, but currently there are indirect IgM assays that perform equally well. 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 tests, hemagglutination inhibition, 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 the demonstration of a rise in the 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 depends 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 U.S. 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.

TEMPORAL PATTERN

In temperate areas, measles disease occurs primarily in the late winter and spring.

COMMUNICABILITY

Measles is highly communicable, with >90% secondary attack rates among susceptible persons. Measles may be transmitted from 4 days prior to 4 days after rash onset. Maximum communicability occurs from onset of prodrome through the first 3-4 days of rash.

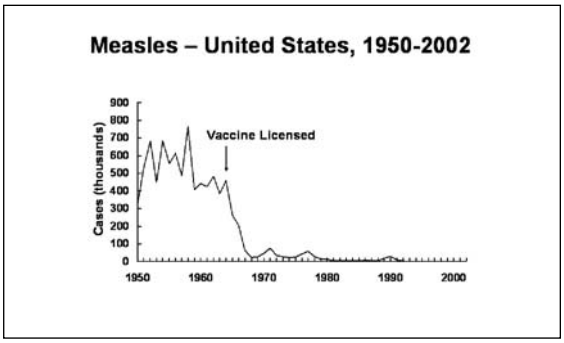
SECULAR TRENDS IN THE UNITED STATES

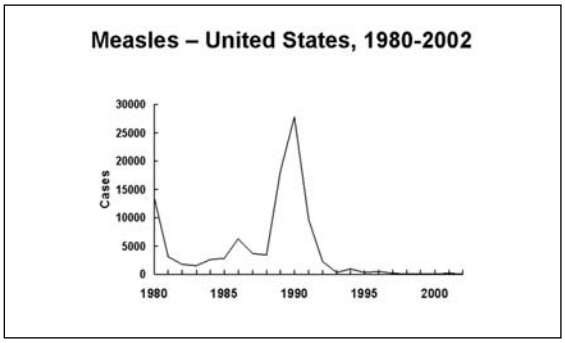
Before 1963, approximately 500,000 cases and 500 deaths were reported annually with epidemic cycles every 2-3 years. However, the actual number of cases was estimated at 3-4 million annually. More than 50% of persons had measles by age 6 and more than 90% had measles by age 15. The highest incidence was in 5-9 year-olds, who generally accounted for more than 50% of reported cases.

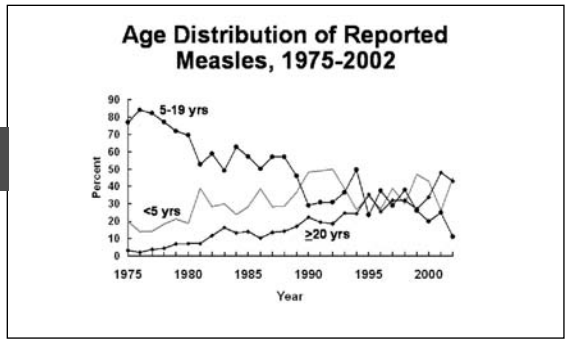
Following licensure of vaccine in 1963, the incidence of measles

Measles Epidemiology

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







Measles Resurgence – United States, 1989-1991

• Cases	55,622
• Age group affected	Children <5 yrs
• Hospitalizations	>11,000
• Deaths	123
• Direct medical costs	>$150 million

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 <5 years of age. A median of 8% of cases were among infants <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) had been appropriately vaccinated. The occurence 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

In 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 in age distribution of cases occurred. 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 <5 years of age. In 1990, 48% of patients were in this age group, the first time that the proportion of cases in children <5 years of age exceeded the proportion of cases in 5-19-year-olds. Thirty-five percent of cases were among school-aged persons (5-19 years old).

Overall incidence rates were highest for Hispanics and blacks and lowest for non-Hispanic whites. Among children <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 = 2.2 per 1,000 cases). Forty-nine percent of deaths were among children <5 years of age. Ninety percent of fatal cases had 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 white children.

Measles susceptibility of infants less than one 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 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 44 cases was reported in 2002. Available epidemiologic and virologic data strongly suggest 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 U.S. from other countries. Due to an aggressive measles vaccination program by the Pan American Health Organization, measles incidence is now 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 over 20 years of age and older accounted for only about 3% of cases. In 1994, adults accounted for 24% of cases, and in 2001, this age group accounted 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.

Measles 1993-2002

- Endemic transmission interrupted
- Record low annual total in 2002 (44 total cases)
- Many cases among adults
- Most cases imported or linked to importation

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 9 persons in New York.

In 2003, a large measles outbreak occurred in the Marshall Islands. As of December 2003, a total of 828 cases had been reported with 83 measles-related hospitalizations and 3 deaths. The outbreak affected predominantly preschool-aged children (40% of cases); adults 20 years and older accounted for 35% of cases. The virus isolated from one case (H1 genotype) was similar to a virus known to circulate in Japan, Korea, and China. A contributing factor for the outbreak was low age-specific measles vaccination coverage in young children, making this outbreak similar to those occurring among this age group on the mainland U.S. in the early 1990s. The outbreak was controlled with aggressive case finding and large vaccination campaigns targeting all persons 6 months to 40 years of age.

CLASSIFICATION OF MEASLES CASES

CLINICAL CLASSIFICATION OF MEASLES CASES

A **suspect case** is a person with a febrile illness accompanied by a generalized maculopapular rash.

Measles Clinical Case Definition

- **Generalized rash lasting ≥3 days, and**
- **Temperature ≥38.3 C (101 F), and**
- **Cough or coryza or conjunctivitis**

A **probable case** meets the **measles case definition** of generalized maculopapular rash lasting ≥3 days, with fever ≥38.3^{o}C (101°F); and cough, or coryza, or conjunctivitis and has no or non-contributory 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 confirmed and probable cases should be reported as soon as possible to the local or state health department.

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 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 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.

Measles Vaccines

1963	Live attenuated and killed 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

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, or combined with mumps and rubella vaccines. The ACIP recommends that combined measles-mumps-rubella vaccine (MMR) be used when any of the individual components is indicated.

Measles vaccine is prepared in chick embryo fibroblast tissue culture. MMR is supplied as a lyophylized (freeze-dried) powder and is reconstituted with sterile, preservative-free water. The vaccine contains a small amount of human albumin, neomycin, sorbitol, and gelatin.

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

IMMUNOGENICITY AND VACCINE EFFICACY

Measles vaccine produces an inapparent or mild, noncommunicable infection. Measles antibodies develop in approximately 95% of children vaccinated at 12 months of age and 98% of children vaccinated at 15 months of age. 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, and possibly other reasons. Most persons who fail to respond to the first dose will respond to a second dose. Studies

MMR Vaccine Failure

- 2%-5% of recipients do not respond to the first dose
- Caused by antibody, damaged vaccine, record errors
- Most persons with vaccine failure will respond to second dose

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 life long in most individuals. 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 only play a minor role in measles transmission and outbreaks.

Measles (MMR) Vaccine Indications

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

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 in 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 2 doses of MMR.

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

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.

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

A second dose of MMR is recommended to produce immunity in those who failed to respond to the first dose. The second dose of MMR vaccine should routinely be given at age 4-6 years, before a child enters kindergarten or first grade. The preadolescent health visit at age 11-12 years can serve as a catch-up opportunity to verify vaccination status and administer MMR vaccine to those children who have not yet received two doses of MMR.

Second Dose Recommendation

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

The second dose of MMR may be administered as soon as one 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 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.

VACCINATION OF ADULTS

Adults born in 1957 or later who do not have a medical contraindication should receive at least one dose of MMR vaccine unless they have documentation of vaccination with at least one dose of measles-, rubella-, and mumps-containing vaccine or other acceptable evidence of immunity to these three diseases. With the exception of women who might become pregnant (see rubella chapter, p. 132) 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 persons include persons attending colleges and other post-high school educational institutions, persons working in medical facilities, and international travelers.

Adults at Increased Risk of Measles

- College students
- International travelers
- Healthcare personnel

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 1989-91 measles resurgence with a total of 36 cases during 1993-96 occurring among persons working in medical facilities. However, transmission in a medical facility occurred in 15 of the 75 measles outbreaks reported during 1993-1996.

Measles Immunity in Healthcare Personnel

- All persons who work in medical facilities should be immune to measles

All persons who work within medical facilities should have evidence of immunity to measles and rubella. Because any healthcare worker (*i.e.*, medical or non-medical, paid or volunteer,

full time or part time, student or non-student, with or without patient-care responsibilities) who is measles or rubella susceptible can contract and transmit these diseases, all medical facilities (*i.e.*, inpatient and outpatient, private and public) should ensure measles and rubella immunity among those who work within their facilities (a possible exception might be a facility that treats only elderly patients considered at low risk for measles and rubella and their complications).

Adequate vaccination for measles and rubella for healthcare workers born during or after 1957 consists of two doses of a live measles-containing vaccine and at least one dose of a live rubella-containing vaccine. Healthcare workers needing a second dose of measles-containing vaccine should be revaccinated at least 4 weeks after their first dose.

Although birth before 1957 is generally considered acceptable evidence of measles and rubella immunity, medical facilities should consider recommending a dose of MMR vaccine to unvaccinated workers born before 1957 who do not have a history of prior measles disease or laboratory evidence of measles immunity, and those without laboratory evidence of rubella immunity.

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

Persons who travel outside of 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

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

Revaccination is recommended for certain persons. The following groups of persons 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 prior to 1968 with an unknown type of vaccine (the vaccine may have been KMV), (5) or vaccinated with IG in addition to a further attenuated strain or vaccine of unknown type (revaccination not necessary if IG was given with Edmonston B vaccine).

POSTEXPOSURE PROPHYLAXIS

Live measles vaccine provides permanent protection and may prevent disease if given within 72 hours of exposure. **Immune globulin (IG)** may prevent or modify disease and provide temporary protection if given within 6 days of exposure. The dose is 0.25 ml/kg body weight, with a maximum of 15 ml intramuscularly. The recommended dose of IG for immunocompromised persons is 0.5ml/kg of body weight (maximum 15 ml) intramuscularly. IG may be especially indicated for susceptible household contacts of measles patients, particularly contacts <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.

MEASLES IMMUNITY

Persons generally can be considered immune to measles if they 1) were born before 1957, 2) have documentation of physician-diagnosed measles, 3) serologic evidence of immunity to measles, or 4) have documentation of adequate vaccination. Criteria for adequate vaccination depend on the person's age. In general, adequate vaccination for preschool-aged children (12 months of age and older) is one dose of MMR. For school- and college-age children, adequate vaccination is two doses of MMR.

Persons working in medical settings are at higher risk of measles than the general population. As a result, adequate vaccination for persons born during or after 1957 who work in medical facilities consists of 2 doses of MMR or other live measles-containing vaccine separated by at least 4 weeks with the first dose administered no earlier than the first birthday. Although birth before 1957 is generally considered acceptable evidence of measles immunity, measles has occurred in some unvaccinated persons born before 1957. Medical facilities should consider recommending a dose of MMR for unvaccinated workers born before 1957 who lack a history of measles disease or laboratory evidence of measles immunity.

Only doses of vaccine with written documentation of the date of receipt should be accepted as valid. Self-reported doses or a parental history 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.

Measles Immunity

- Born before 1957
- Documentation of physician-diagnosed measles
- Serologic evidence of immunity
- Documentation of receipt of measles-containing vaccine

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

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 occur 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.

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 $\geq 103^{o}F$ ($\geq 39.4^{o}C$) 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.

MMR vaccine may rarely cause **thrombocytopenia** (low platelet count) within the 2 months after vaccination. Estimates of the frequency of clinically apparent thrombocytopenia from Europe are 1 case per 30,000 to 40,000 vaccinated susceptible persons, with a temporal clustering of cases occurring 2 to 3 weeks after vaccination. The clinical course of these cases was usually transient and benign, although hemorrhage occurred rarely. The risk for thrombocytopenia during rubella or measles infection is much greater than the risk after vaccination. Based on case reports, the risk for MMR-associated thrombocytopenia may be higher for persons who have previously had immune thrombocytopenic purpura, particularly for those who had thrombocytopenic purpura after an earlier dose of MMR vaccine.

Transient **lymphadenopathy** sometimes occurs following receipt of MMR or other rubella-containing vaccine and **parotitis** has been reported rarely following receipt of MMR or other mumps-containing vaccine.

Arthralgias and other **joint symptoms** are reported in up to 25% of susceptible adult women given MMR vaccine. This adverse reaction is associated with the rubella component (see Rubella, Chapter 11, 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 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 U.S. 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.

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, recent 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.

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

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

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

death in at least six severely immunocompromised persons. For this reason, **patients who are severely immunocompromised for any reason should not be given MMR vaccine**. Healthy susceptible close contacts of severely immunocompromised persons should be vaccinated.

In general, persons receiving **large daily doses of corticosteroids** (≥2 mg/kg per day or ≥20 mg 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 one month after cessation of high dose therapy. Persons receiving low dose or short course (<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 two weeks after completion of therapy.

Patients with leukemia in remission who have not received chemotherapy for at least 3 months may receive MMR or its component vaccines.

Measles disease may be severe in persons with **HIV infection**. Available data indicate that vaccination with MMR has not been associated with severe or unusual adverse reactions in HIV-infected persons without evidence of severe immunosuppression, although antibody responses have been variable. MMR vaccine is recommended for all asymptomatic HIV-infected persons, and should be considered for symptomatic persons who are not severely immunosuppressed. Asymptomatic children do not need to be evaluated and tested for HIV infection before MMR or other measles-containing vaccines are administered. A theoretical risk of an increase (probably transient) in HIV viral load following MMR vaccination exists because such an effect has been observed with other vaccines. The clinical significance of such an increase is not known.

Measles Vaccine and HIV Infection

- **MMR recommended for persons with asymptomatic and mildly symptomatic HIV infection**
- **NOT recommended for those with evidence of severe immunosuppression**
- **Prevaccination HIV testing not recommended**

MMR and other measles-containing vaccines are not recommended for HIV-infected persons with evidence of severe immunosuppression (see table), primarily because of a report of

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%

measles pneumonitis in a recipient of measles vaccine who had severe HIV-related immunosuppression.

Persons with **moderate or severe acute illness** should not be vaccinated until the illness has improved or resolved. This precaution is intended to prevent complicating the management of an ill patient

with a potential vaccine adverse event, such as fever. Minor illness (*e.g.*, otitis media, mild upper respiratory infections), concurrent antibiotic therapy, and exposure or recovery from other illness are not contraindications to measles vaccination. One recent study suggested that seroconversion to measles vaccine was reduced in children with upper respiratory infections. However, multiple previous and subsequent studies have not confirmed this finding.

Receipt of antibody-containing blood products (*e.g.*, immune globulin, whole blood or packed red blood cells, intravenous immune globulin) may interfere with seroconversion to measles vaccine. The length of time that such passively acquired antibody persists depends on the concentration and quantity of blood product received. For instance, vaccination is recommended to 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 the chapter on General Recommendations on Immunization, and Measles Vaccine and the Antibody Table in Appendix A.

Persons who have a history of thrombocytopenic purpura or **thrombocytopenia** may be at increased risk for developing clinically significant thrombocytopenia after MMR vaccination. No deaths have been reported as a direct consequence of vaccine-induced thrombocytopenia. The decision to vaccinate with MMR depends on the benefits of immunity to measles, mumps, and rubella and the risks for recurrence or exacerbation of thrombocytopenia after vaccination or during natural infection with measles or rubella. The benefits of immunization are usually greater than the potential risks, and administration of MMR vaccine is justified, because of the even greater risk for thrombocytopenia after measles or rubella disease. However, deferring a subsequent dose of MMR vaccine may be prudent if the previous episode of thrombocytopenia occurred within 6 weeks after the previous dose of the vaccine. Serologic evidence of measles immunity in such persons may be sought in lieu of MMR vaccination.

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

PPD and Measles Vaccine

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

vaccine. This option is the least favored because it will delay receipt of the vaccine.

VACCINE STORAGE AND HANDLING

Measles vaccine and MMR must be shipped with refrigerant to maintain 10°C (50°F) 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 (2°-8°C [35°-46°F]), but may be frozen. Diluent may be stored at refrigerator temperature or at room temperature.

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.

MEASLES VIRUS ISOLATION

The availability of a sensitive cell line (B95a) for isolation of measles virus from clinical specimens and the establishment of automated DNA sequencing techniques have allowed for rapid genetic characterization of a large number of wild type strains of measles virus. This database of sequence information now makes it possible to use molecular epidemiological techniques to identify the source of wild type viruses and to rapidly differentiate between wild type and vaccine strains. With progress toward elimination of measles in the U.S., it is critical to examine virus isolates from as many outbreaks as possible in order to identify the source of the virus.

Virus isolation and genetic characterization can take several months to complete. Therefore, **diagnosis of measles should always be based on detection of measles-specific IgM in serum**. The IgM-capture EIA test can be completed in one day. Specimens for virus isolation can and should be taken at the same time that serum is obtained, since a delay in collection will reduce the chance of isolating the virus. However, **urine or nasopharyngeal or throat swab specimens should not be substituted for serum specimens for measles diagnosis**.

A detailed protocol for collection and transport of specimens for measles virus is available on the CDC web site at http://www.cdc.gov/ncidod/dvrd/revb/measles/viral_isolation.htm.

SELECTED REFERENCES

American Academy of Pediatrics. Measles. In: Pickering L ed. *Red Book: 2003 Report of the Committee on Infectious Diseases*. 26th ed. Elk Grove Village, IL: American Academy of Pediatrics, 2003:419-29.

Atkinson WL, Markowitz LE, Adams NC, Seastrom GR. Transmission of measles in medical settings--United States, 1985-1989. *Am J Med* 1991;91(Suppl 3B):320-4.

Atkinson WL, Orenstein WA, Krugman S. The resurgence of measles in the United States, 1989-1990. *Ann Rev Med* 1992;43:451-63.

Bellini WJ and Rota PA. Genetic diversity of wild type measles viruses: implications for global measles elimination programs. *Emerg Infect Dis* 1998;4:29-35.

CDC. Measles, mumps, and rubella - vaccine use and strategies for elimination of measles, rubella, and congenital rubella syndrome and control of mumps. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 1998;47(RR-8):1-57.

CDC. Immunization of health-care workers. Recommendations of the Advisory Committee on Immunization Practices (ACIP) and the Hospital Infection Control Practices Advisory Committee (HICPAC). *MMWR* 1997;46(RR-18):1-42.

CDC. Measles-United States, 2000. *MMWR* 2002;51:120-3.

CDC. Update: global measles control and mortality reduction - worldwide, 1991-2001. *MMWR* 2003;52:471-5.

Black FL. Measles. In: Evans AS, Kraslow RA, eds. *Viral Infections of Humans. Epidemiology and Control*. 4th ed. New York, NY: Plenum Medical Book Company; 1997:507-29.

Halsey NA, Hyman SL, and the Conference Writing Panel. Measles-mumps-rubella vaccine and autistic spectrum disorder: report from the New Challenges in Childhood Immunizations conference convened in Oak Brook, IL, June 12-13, 2000. *Pediatrics* 2001;107(5).

Institute of Medicine immunization safety reviews: measles-mumps-rubella vaccine and autism. Washington DC, National Academy Press, 2001.

Vitek CR, Aduddel, M, Brinton MJ. Increased protection during a measles outbreak of children previously vaccinated with a second dose of measles-mumps-rubella vaccine. *Pediatr Infect Dis J* 1999;18:620-3.

Mumps is an acute viral illness. Although parotitis and orchitis were described by Hippocrates in the 5th century BCE, until relatively recently mumps was viewed primarily as an illness that affected armies during times of mobilization. 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 filtrable agent present in saliva. This agent was later shown to be a virus. Mumps was a frequent cause of outbreaks among military personnel in the prevaccine era, and was one of the most common causes of aseptic meningitis and sensorineural deafness in childhood. During World War I, only influenza and gonorrhea were more common causes of hospitalization among soldiers. Outbreaks of mumps have been reported among military personnel as recently as 1986.

Mumps

- Acute viral illness
- Parotitis and orchitis described by Hippocrates in 5th century B.C.
- 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. The virus replicates in the nasopharynx and regional lymph nodes. After 12-25 days a viremia occurs which lasts from 3 to 5 days. During the viremia, the virus spreads to multiple tissues, including the meninges, and glands such as the salivary, pancreas, testes, and ovaries. Inflammation in infected tissues leads to characteristic symptoms of parotitis and aseptic meningitis.

Mumps Pathogenesis

- Respiratory transmission of virus
- Replication in nasopharynx and regional lymph nodes
- Viremia 12-25 days after exposure with spread to tissues
- Multiple tissues infected during viremia

CLINICAL FEATURES

The incubation period of mumps is 14-18 days (range, 14-25 days). The **prodromal symptoms** are nonspecific, and include myalgia, anorexia, malaise, headache, and low-grade fever.

Parotitis is the most common manifestation, and occurs in 30%-40% of infected persons. Parotitis may be unilateral or bilateral and any combination of single or multiple salivary glands may be affected. Parotitis tends to occur within the first 2 days and may first be noted as earache and tenderness on palpation of the angle of the jaw. Symptoms tend to decrease after 1 week and have usually resolved after 10 days.

Mumps Clinical Features

- Incubation period 14-18 days
- Nonspecific prodrome of low-grade fever, headache, malaise, myalgias
- Parotitis in 30%-40%
- Up to 20% of infections asymptomatic
- May present as lower respiratory illness, particularly in preschool-aged children

Up to 20% of mumps infections are asymptomatic. An additional 40%-50% may have only nonspecific or primarily respiratory symptoms.

COMPLICATIONS

Mumps Complications

CNS involvement	15% of clinical cases
Orchitis	20%-50% in post-pubertal males
Pancreatitis	2%-5%
Deafness	1/20,000
Death	1-3/10,000

Central nervous system (CNS) involvement in the form of aseptic meningitis is common, occurring asymptomatically (inflammatory cells in cerebrospinal fluid) in 50%-60% of patients. Symptomatic meningitis (headache, stiff neck) occurs in up to 15% of patients and resolves without sequelae in 3-10 days. Adults are at higher risk for this complication than children, and boys are more commonly affected than girls (3:1 ratio). Parotitis may be absent in up to 50% of such patients. Encephalitis is rare (less than 2 per 100,000).

Orchitis (testicular inflammation) is the most common complication in postpubertal males. It occurs in up to 50% of postpubertal males, usually after parotitis, but may precede it, begin simultaneously, or occur alone. It is bilateral in up to 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. While some single instances of **diabetes mellitus** have been reported, a causal relationship 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 (EKG) 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 1 death from mumps per year was reported in 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, including saliva, urine, and cerebrospinal fluid. If virus isolation is attempted, the specimen should be collected within the first 5 days of illness.

Serology is the most common method used to diagnose mumps. Complement fixation (CF) and hemagglutination inhibition (HI) antibody tests for mumps are relatively insensitive, and results may not be reliable. Tests that have demonstrated reliability include neutralization, enzyme immunoassay (EIA), and radial hemolysis antibody tests. Neutralization assays are time consuming and not generally available for routine diagnostic use.

The EIA is widely available commercially and is more sensitive than the CF, HI, or radial hemolysis. 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. IgG testing usually requires two specimens separated by several weeks. The convalescent (second) specimen should show a significant increase in antibody compared with the acute (first) specimen.

Mumps Laboratory Diagnosis

- Isolation of mumps virus
- 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. While persons with asymptomatic or nonclassical infection can transmit the virus, no carrier state is known to exist.

TRANSMISSION

Transmission of mumps occurs through airborne transmission or direct contact with infected droplet nuclei or saliva.

TEMPORAL PATTERN

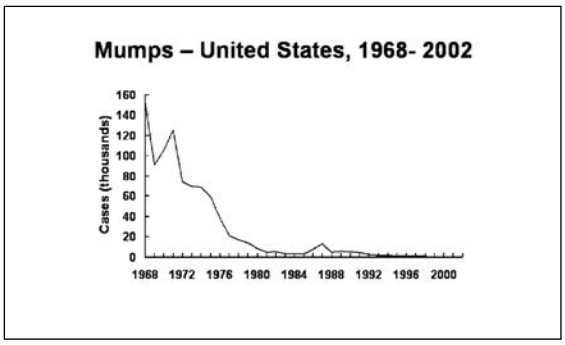
Mumps incidence peaks predominantly in late winter-spring, but the disease has been reported throughout the year.

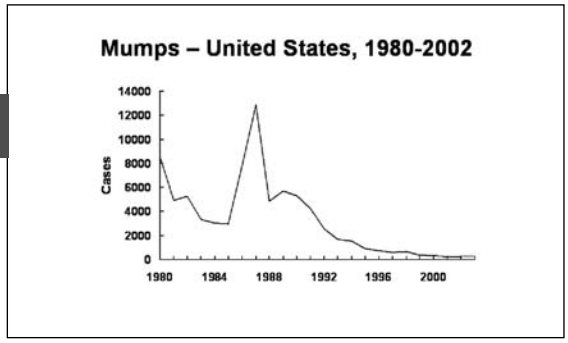
COMMUNICABILITY

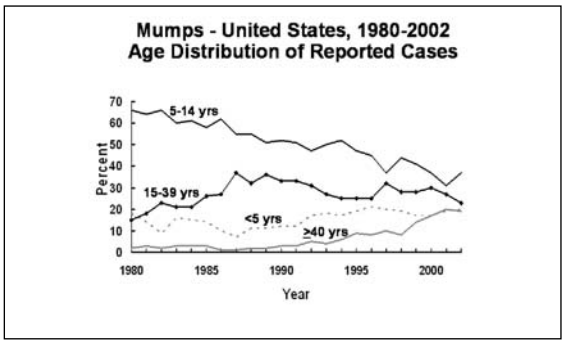
Contagiousness is similar to that of influenza and rubella, but less than that for measles or varicella. The infectious period is considered to be from 3 days before to the 4th day of active disease; virus has been isolated from saliva 7 days before to 9 days after onset of parotitis.

Mumps Epidemiology

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







Mumps Clinical Case Definition

- **Acute onset of unilateral or bilateral tender, self-limited swelling of the parotid or other salivary gland lasting >2 days without other apparent cause.**

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. The peak was 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 recommendations for routine mumps vaccination. Mumps incidence in this period correlated with 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, there has been a steady decline in reported mumps cases, from 5,712 cases to a provisional total of 231 cases in 2001, the lowest annual total ever reported. As more children, adolescents, and adults received two doses of MMR vaccine, the number of reported cases of mumps has continued to decrease. Because many reported cases are not confirmed by laboratory testing, it is likely that many of the cases lacking laboratory confirmation are, in fact, not due to infection with mumps virus. Experience in states that have conducted more complete laboratory testing for confirmation suggests that case investigation, combined with appropriate laboratory testing, will result in many suspected cases being discarded and a resulting decrease in reported mumps morbidity. Laboratory confirmation helps ensure that only true mumps cases are reported.

Prior to 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 >2 days without other apparent cause.

MUMPS VACCINE

CHARACTERISTICS

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

Mumps vaccine is available as a single antigen preparation, combined with rubella vaccine, or combined with measles and rubella vaccines. The ACIP recommends that combined measles-mumps-rubella vaccine (MMR) be used when any of the individual components is indicated.

Mumps vaccine is prepared in chick embryo fibroblast tissue culture. MMR is supplied as a lyophilized (freeze-dried) powder and is 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 — Life long
- Schedule — ≥1 Dose
- Should be administered with measles and rubella (MMR)

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. Clinical efficacy has been estimated to be 95% (range, 90%-97%). The duration of vaccine-induced immunity is believed to be greater than 25 years, and is probably life long in most vaccine recipients.

VACCINATION SCHEDULE AND USE

At least one dose of mumps vaccine, as combination MMR vaccine, separated by at least 4 weeks, are routinely recommended for all children. All persons born in 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. Mumps-containing vaccine given before 12 months of age should not be counted as part of the series. Children vaccinated with mumps-containing vaccine before 12 months of age should be revaccinated with two doses of MMR vaccine, the first of which should be administered when the child is at least 12 months of age.

Mumps (MMR) Vaccine Indications

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

A second dose of MMR is recommended to produce immunity to measles in those who failed to respond to the first dose. Data indicate that almost all of the 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 of MMR.

The second dose of MMR is not generally considered a booster dose because a primary immune response to the first dose provides long-term protection. Although a second dose of vaccine may increase antibody titers in some persons who responded to the first dose, available data indicate that these increased antibody titers are not sustained. The combined MMR vaccine is recommended for both doses to assure immunity to all three viruses.

The second dose of MMR vaccine should be given routinely at age 4-6 years, before a child enters kindergarten or first grade. The adolescent health visit at age 11-12 years can serve as a catch-up opportunity to verify vaccination status and administer MMR vaccine to those children who have not yet received two doses of MMR. The second dose of MMR may be administered as soon as 4 weeks (*i.e.*, 28 days) after the first dose.

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

MUMPS IMMUNITY

Mumps Immunity

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

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. The 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 unless they have other evidence of mumps immunity.

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

POSTEXPOSURE PROPHYLAXIS

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

ADVERSE REACTIONS FOLLOWING VACCINATION

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

Rare cases of **CNS dysfunction**, including cases of deafness, within 2 months of mumps vaccination have been reported. The calculated incidence of CNS reactions is approximately one per million doses of antigen, a rate lower than the reported background encephalitis rate of 2-6/10,000. 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 are transient and generally mild.

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

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, recent 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 for theoretic reasons. 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** result-

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

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

ing from leukemia, lymphoma, generalized malignancy, immune deficiency disease, or immunosuppressive therapy should not be vaccinated. However, treatment with low dose (<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 stopped for 1 month may be vaccinated.

Persons with **moderate or severe acute illness** should not be vaccinated until the illness has resolved. Minor illness (*e.g.*, otitis media, mild upper respiratory infections), concurrent antibiotic therapy, and exposure or recovery from other illnesses, are not contraindications to mumps vaccination.

Receipt of **antibody-containing blood products** (*e.g.*, immune globulin, whole blood or packed red blood cells, intravenous immune globulin) may interfere with seroconversion following mumps vaccination. Vaccine should be given 2 weeks before, or deferred for at least 3 months following, administration of an antibody-containing blood product (see chapter on General Recommendations on Immunization, p. 7, for details).

A family history of diabetes is **not** a contraindication for vaccination.

VACCINE STORAGE AND HANDLING

Measles-mumps-rubella (MMR) vaccine must be shipped with refrigerant to maintain 10°C (50°F) 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 (2°-8°C [35°-46°F]), but may be frozen. Diluent may be stored at refrigerator temperature or at room temperature.

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.

SELECTED REFERENCES

American Academy of Pediatrics. Mumps. In: Pickering L ed. *Red Book: 2003 Report of the Committee on Infectious Diseases*. 26th ed. Elk Grove Village, IL: American Academy of Pediatrics, 2003:439-43.

CDC. Measles, Mumps, and Rubella - vaccine use and strategies for elimination of measles, rubella, and congenital rubella syndrome and control of mumps. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 1998;47(RR-8):1-57.

Cochi SL, Preblud SR, Orenstein WA. Perspective on the relative resurgence of mumps on the United States. *Am J Dis Child* 1988;142:499-507.

Holmes SJ. Mumps. In: Evans AS, Kaslow RA, eds. *Viral Infections of Humans. Epidemiology and Control*. 4th ed. New York, NY: Plenum Medical Book Company; 1997:531-50..

Hirsh BS, Fine PEM, Kent WK, et al. Mumps outbreak in a highly vaccinated population. *J Pediatr* 1991;119:187-93.

Orenstein WA, Hadler S, Wharton M. Trends in vaccine-preventable diseases. *Semin Pediatr Infect Dis* 1997;8:23-33.

Plotkin SA. Mumps vaccine. In: Plotkin SA, Orenstein, WA, eds. *Vaccines*. 4th ed. Philadelphia: Saunders; 2003: 441-70.

Van Loon FPL, Holmes SJ, Sirotkin BI, et al. Mumps surveillance—United States, 1988 - 1993. In: CDC Surveillance Summaries, August 11, 1995. *MMWR* 1995;44:1-14.

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 acute cases.

Following a widespread epidemic of rubella infection in 1940, Norman Gregg, an Australian ophthalmologist, reported in 1941 the occurrence of congenital cataracts among 78 infants born following maternal rubella infection in early pregnancy. This was the first reported recognition of congenital rubella syndrome (CRS).

Rubella

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

RUBELLA VIRUS

Rubella virus was first isolated in 1962 by Parkman and Weller. Rubella virus is classified as a togavirus, genus *Rubivirus*. It is most closely related to group A arboviruses, such as Eastern and Western Equine Encephalitis viruses. It is an enveloped RNA virus, with a single antigenic type that does not cross-react with other members of the togavirus group.

Rubella virus is relatively unstable and is inactivated by lipid solvents, trypsin, formalin, ultraviolet light, low pH and heat, and amantadine.

Rubella Virus

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

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 to 23 days. Symptoms are often mild, and up to 50% of infections may be subclinical or inapparent. In children, **rash** is usually the first manifestation and a prodrome is rare. In older children and adults, there is often a 1-5 day prodrome with low-grade fever, malaise, lymphadenopathy, and upper respiratory symptoms preceding the rash. The rash of rubella usually occurs initially on the face and then progresses from head to foot. It lasts about 3 days and is occasionally pruritic. The rash is fainter than measles rash and does not coalesce. The rash is more prominent after a hot shower or bath.

Lymphadenopathy may begin a week before the rash and last several weeks. Postauricular, posterior cervical, and suboccipital nodes are

Rubella Clinical Features

- Incubation period 14 days (range 12-23 days)
- Prodrome of low grade fever
- Lymphadenopathy in second week
- Maculopapular rash 14-17 days after exposure

commonly involved.

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

COMPLICATIONS

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

Rubella Complications

Arthralgia or arthritis	
children	rare
adult female	up to 70%
Thrombocytopenic purpura	1/3000 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 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 1 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**.

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

CONGENITAL RUBELLA SYNDROME (CRS)

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

A rubella epidemic in the United States in 1964-1965 resulted in 12.5 million cases of rubella infection and about 20,000 newborns with CRS. The estimated cost of the epidemic was $840 million. This does not include the emotional toll on the families involved. The estimated lifetime cost of one case of CRS today is estimated to be in excess of $200,000.

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

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. Up to 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 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 4th 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 (SSPE) has been observed in some older children with CRS.

CRS infants may have low hemagglutination inhibition (HI) titers, 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 may mimic rubella infection and up to 50% of rubella infections may be subclinical. The only reliable evidence of acute rubella infection is the presence of rubella-specific IgM antibody, demonstration of a significant rise in IgG antibody from paired acute and convalescent sera, or a positive viral culture for rubella, or detection of rubella virus by RT-PCR.

Rubella Laboratory Diagnosis

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

Rubella virus can be isolated from nasal, blood, throat, urine and cerebrospinal fluid specimens from rubella and CRS cases. 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 serum specimens or by the presence of serum rubella IgM. Sera 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 assays (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 sera are tested). A four-fold rise or greater in HI 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.

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

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 subclinical or asymptomatic cases (up to 50% of all rubella virus infections).

TEMPORAL PATTERN

In temperate areas, incidence is usually highest in late winter and early spring.

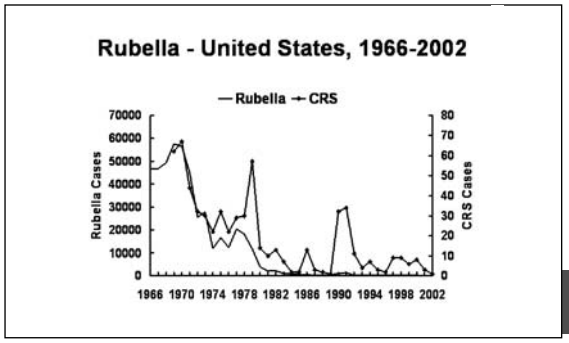
COMMUNICABILITY

Rubella is only moderately contagious. The disease is most contagious when the rash is erupting, but virus may be shed from 7 days before to 5-7 days or more after rash onset.

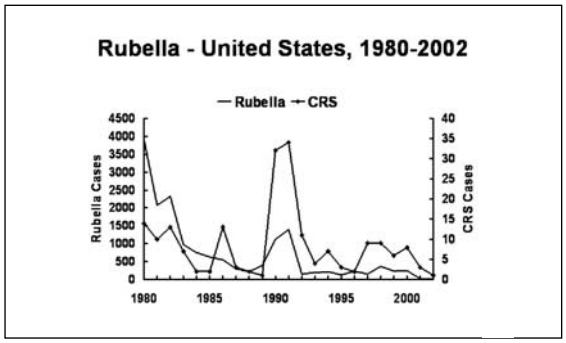
Infants with CRS shed large quantities of virus from body secretions for up to one year and can therefore transmit rubella to persons caring for them who are susceptible to the disease.

SECULAR TRENDS IN THE UNITED STATES

Rubella and congenital rubella syndrome became nationally notifiable diseases in 1966. The largest annual total of cases of rubella in the United States was in 1969, when 57,686 cases were reported (58 cases per 100,000 population). Following vaccine licensure in 1969, rubella incidence fell rapidly. By 1983, fewer than 1,000 cases per year were reported (<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 2002 a record low annual total of 18 cases was reported.

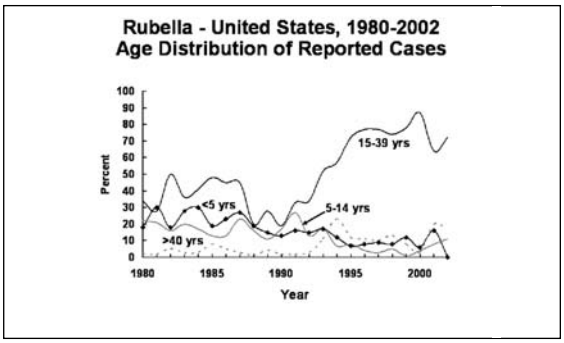


Until recently, there was no predominant age group for rubella cases. From 1982 through 1992, approximately 30% of cases occurred in each of three age groups: <5, 5-14, and 15-39 years. Adults >40 years of age typically accounted for <10% of cases. However, since 1993, persons 15-39 years of age have accounted for more than half of the cases. In 2002, this age group accounted for 72% of all reported cases.



Most reported rubella in the U.S. since the mid-1990s has occurred among Hispanic young adults who were born in areas where rubella vaccine is routinely not given.

In the prevaccine era, epidemics of rubella occurred every 6-9 years, with the last major U.S. epidemic occurring in 1964-1965. No large epidemics have occurred since the vaccine was licensed for use in 1969. However, outbreaks continue to occur among groups of susceptible persons who congregate in locations that increase their exposure and among persons with religious and philosophic exemption to vaccination. Several recent outbreaks have occurred in workplaces where most employees are foreign-born, particularly from Latin America.



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 U.S., the incidence of CRS has only paralleled the decrease in rubella cases since the mid-1970s. The fall in CRS since the mid-1970s was due to an increased effort to vaccinate suscepti-

Rubella and CRS in the United States

- Most reported rubella in the U.S. since the mid-1990s has occurred among foreign-born Hispanic adults
- Rubella outbreaks have occurred in workplaces where most employees are foreign-born
- 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 >37.2 C (>99 F), if measured, and
- Arthralgia or arthritis, or lymphadenopathy, or conjunctivitis

ble 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. A provisional total of 2 CRS cases were reported in 2001. Since 1997, the mothers of the majority of infants with CRS were Hispanic women, most of whom were born in Latin American or Carribean 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 >37.2°C (>99°F), 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 testing, 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 (CRS)

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 (A) above or one

complication from (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 U.S. in 1969: HPV-77:DE-5 (duck embryo), HPV-77:DK-12 (dog kidney), and Cendehill (rabbit kidney) strains. The HPV-77:DK-12 was later removed from the market because there was a higher rate of joint complaints following vaccination with this strain. In January 1979, the RA 27/3 (human diploid fibroblast) strain (Meruvax-II) was licensed and all other strains were discontinued.

Rubella Vaccine

Vaccine	Trade Name	Licensure
GMK-3:RK53	Cendevax	1969
HPV-77:DK12	Rubelogen	1969
HPV-77:DE5	Meruvax	1969
RA 27/3*	Meruvax II	1979

*Only vaccine currently licensed in U.S.

CHARACTERISTICS

The RA 27/3 rubella vaccine is a live attenuated virus. It was first isolated in 1965 at the Wistar Institute from a rubella-infected aborted fetus. The virus was attenuated by 25-30 passages in tissue culture, using human diploid fibroblasts. It does not contain duck, chicken or egg protein.

Vaccine virus is not communicable, except in the setting of breastfeeding (see Contraindications, below), even though virus may be cultured from the nasopharynx of vaccinees.

Rubella vaccine is available as a single antigen preparation, combined with mumps vaccine, or combined with measles and rubella vaccines. The ACIP recommends that combined measles-mumps-rubella vaccine (MMR) be used when any of the individual components is indicated.

Rubella Vaccine

- Composition — Live virus (RA 27/3 strain)
- Efficacy — 95% (Range, 90%-97%)
- Duration of Immunity — Lifelong
- Schedule — ≥1 Dose
- Should be administered with measles and mumps as MMR

IMMUNOGENICITY AND VACCINE EFFICACY

RA 27/3 rubella vaccine is safe and more immunogenic than previously used rubella vaccines. 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.

Several reports indicate that viremic reinfection following exposure may occur among 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.

Rubella Vaccine (MMR) Indications

- All infants >12 months of age
- Susceptible adolescents and adults without documented evidence of rubella immunity
- Emphasis on non-pregnant women of childbearing age, particularly those born outside the U.S.

VACCINATION SCHEDULE AND USE

At least one dose of rubella vaccine, as combination MMR vaccine, separated by at least 4 weeks, are routinely recommended for all children. All persons born in or after 1957 should have documentation of at least one dose of MMR. The **first dose of MMR** should be given on or after the first birthday. Any dose of rubella-containing vaccine given before 12 months of age should not be counted as part of the series. Children vaccinated with rubella-containing vaccine before 12 months of age should be revaccinated with two doses of MMR vaccine, the first of which should be administered when the child is at least 12 months of age.

A **second dose of MMR** is recommended to produce immunity to measles in those who failed to respond to the first dose. Data indicate that almost all of the 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 of MMR. 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 assure immunity to all three viruses.

The second dose of MMR vaccine should routinely be given at age 4-6 years, before a child enters kindergarten or first grade. The adolescent health visit at age 11-12 years can serve as a catch-up opportunity to verify vaccination status and administer MMR vaccine to those children who have not yet received two doses of MMR (with the first dose administered no earlier than the first birthday). The second dose of MMR may be administered as soon as one month (*i.e.,* minimum of 28 days) after the first dose.

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

Adults born in 1957 or later who do not have a medical contraindication should receive at least one dose of MMR vaccine unless they have documentation of vaccination with at least one dose of measles-, rubella-, and mumps-containing vaccine or other acceptable evidence of immunity to these three diseases. Some adults at high risk of measles exposure may require a second dose of measles vaccine. This second dose should be administered as combined MMR vaccine (see Measles chapter for details). **Efforts should be made to identify and vaccinate susceptible adolescents and adults, particularly women of childbearing age who are not pregnant.** Particular emphasis should be placed on vaccinating both males and females in colleges, places of employment, and healthcare settings.

RUBELLA IMMUNITY

Persons generally can be considered immune to rubella if they have documentation of vaccination with at least one dose of MMR 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 unless they have evidence of adequate vaccination or subsequent serologic testing indicates rubella immunity. 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

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. Laboratories that regularly perform antibody testing are generally the most reliable because their reagents and procedures are strictly standardized.

Occasionally, an individual 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.

Although birth before 1957 is generally considered acceptable evidence of measles and rubella immunity, medical facilities should consider recommending a dose of MMR vaccine to unvaccinated 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.

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 performed without prior testing. Serologic testing for immunity to measles and rubella is not necessary for persons documented to be appropriately vaccinated or who have other acceptable evidence of immunity.

Neither rubella vaccine nor immune globulin is effective for **postexposure prophylaxis of rubella**. Vaccination after exposure is not harmful and may possibly avert later disease.

ADVERSE REACTIONS FOLLOWING VACCINATION

Rubella is a very safe vaccine. Most adverse reactions reported following MMR vaccination are attributable to the measles component (such as fever and rash). The most common complaints following rubella vaccination are fever, lymphadenopathy, and arthralgia. These adverse reactions only occur in susceptible persons and are more common in adults, especially in women.

MMR Adverse Reactions

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

Rubella Vaccine Arthropathy

- Acute joint symptoms in about 25% of susceptable adult women
- Frank arthritis occurs in about 10%
- Rare reports of chronic or persistent symptoms
- Population-based studies have not confirmed association

Joint symptoms, such as arthralgia (joint pain) and arthritis (joint redness and/or swelling), are associated with the rubella component of MMR. Arthralgia and transient arthritis occur more frequently in susceptible adults than in children and more frequently in susceptible women than in men. Acute arthralgia or arthritis are 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 and/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

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** 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 (<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 stopped 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 resolved. Minor illness (*e.g.*, otitis media, mild upper respiratory infections), concurrent antibiotic therapy, and exposure or recovery from other illness 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 the chapter on 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 assure 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.

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

RUBELLA VACCINATION OF WOMEN OF CHILDBEARING AGE

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 who are pregnant or intend to become pregnant within 4 weeks should not receive rubella vaccine. The Advisory Committee on Immunization Practices (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 advised of the theoretical risks of vaccination during pregnancy and the importance of not becoming pregnant during the 4 weeks following vaccination. ACIP does not recommend routine pregnancy screening of women before rubella vaccination.

If a pregnant woman is inadvertently vaccinated or if she becomes pregnant within 4 weeks after vaccination, she should be counseled about the concern for the fetus (see below), but MMR vaccination during pregnancy should not ordinarily be a reason to consider termination of the pregnancy.

Evaluation of the effectiveness of prevaccine pregnancy prevention counseling in women of childbearing age in Hawaii revealed that the pregnancy rate for all women 15-44 years old in Hawaii was 122.8/1,000/year and the pregnancy rate among vaccinees 15-44 years of age who were counseled was 14.0/1,000/year. The efficacy of counseling is 88.6% ([122.8-14.0]/[122.8 x 100]).

Vaccination in Pregnancy Study 1971-1989

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

While pregnancy is a contraindication to rubella vaccination, some women have been inadvertently vaccinated while pregnant or soon before conception. When rubella vaccine was licensed, this situation was of concern because of the known teratogenicity of the wild virus strain. To define the risk, if any, the Centers for Disease Control and Prevention (CDC) maintained a registry from 1971-1989 of women vaccinated during pregnancy to determine whether CRS would occur in infants of such mothers.

Subclinical fetal infection has been detected serologically in approximately 1%-2% of infants born to susceptible vaccinees, regardless of the vaccine strain. However, based on data collected by the CDC in the **Vaccine in Pregnancy (VIP) Registry**, no evidence of CRS occurred 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 pregnant women should **not** be vaccinated, because of the small theoretical risk to the fetus of a vaccinated woman.

VACCINE STORAGE AND HANDLING

Measles-mumps-rubella (MMR) vaccine must be shipped with refrigerant to maintain 10°C (50°F) 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 (2°-8°C [35°-46°F]), but may be frozen. Diluent may be stored at refrigerator temperature or at room temperature.

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.

STRATEGIES TO DECREASE RUBELLA AND CRS

CRS ELIMINATION

Although the CRS case count 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 achieved by expanding and intensifying 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 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 (volunteers, trainees, nurses, physicians, etc.) 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.

Rubella Vaccine
Recommendations for Increasing Coverage

- Continued routine vaccination of children at age ≥12 months with vaccination required for school entry
- Screen and vaccinate susceptible persons
  - healthcare workers
  - college entry
  - prenatal with postpartum vaccination
  - other healthcare visits
  - workplace

USE OF COMBINATION VACCINES

The use of combination vaccines such as MR and MMR vaccines and the two-dose schedule of MMR vaccine for measles control will increase the level of rubella seropositivity in children and adults. Persons already immune to rubella should not have adverse events attributable to rubella vaccine; those not already immune are in need of vaccination against rubella.

SELECTED REFERENCES

American Academy of Pediatrics. Rubella. In: Pickering L ed. *Red Book: 2003 Report of the Committee on Infectious Diseases*. 26th ed. Elk Grove Village, IL: American Academy of Pediatrics, 2003:536-41.

CDC. Measles, mumps, and rubella - vaccine use and strategies for elimination of measles, rubella, and congenital rubella syndrome and control of mumps. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 1998;47(RR-8):1-57.

CDC. Immunization of health-care workers. Recommendations of the Advisory Committee on Immunization Practices (ACIP) and the Hospital Infection Control Advisory Committee (HICPAC). *MMWR* 1997;46(RR-18):1-42.

CDC. Control and prevention of rubella: evaluation and management of suspected outbreaks, rubella in pregnant women, and surveillance for congenital rubella syndrome. *MMWR* 2001;50(RR-12):1-30.

CDC. Rubella vaccination during pregnancy--United States, 1971-1988. *MMWR* 1989;38:289-93.

CDC. Revised ACIP recommendations for avoiding pregnancy after receiving rubella-containing vaccine. *MMWR* 2001;50:1117.

Frenkel LM, Nielsen K, Garakian A, et all. A search for persistent rubella virus infection in persons with chronic symptoms after rubella and rubella immunization and in patients with juvenile rheumatoid arthritis. *Clin Infect Dis* 1996;22:287-94.

Mellinger AK, Cragan JD, Atkinson WL, et al. High incidence of congenital rubella syndrome after a rubella outbreak. *Pediatr Infect Dis J* 1995;14:573-78.

Orenstein WA, Hadler S, Wharton M. Trends in vaccine-preventable diseases. *Semin Pediatr Infect Dis* 1997;8:23-33.

Reef SE, Frey TK, Theall K, et al. The changing epidemiology of rubella in the 1990s. *J Am Med Assoc* 2002;287:464-72.

Varicella is an acute, contagious 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 susceptible children acquired varicella after contact with herpes zoster. VZV was isolated from vesicular fluid of both chickenpox and zoster lesions in cell culture by Thomas Weller in 1954. Subsequent laboratory studies of the virus led to the development of a live attenuated varicella vaccine in Japan in the 1970s. The vaccine was licensed for use in healthy children and adults in the United States in March 1995.

Varicella

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

VARICELLA ZOSTER VIRUS (VZV)

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

Varicella Zoster Virus

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

PATHOGENESIS

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

Varicella Pathogenesis

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

CLINICAL FEATURES

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

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, pruritic, and rapidly progresses from macules to papules to vesicular lesions before crusting. The rash usually

Varicella Clinical Features

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

appears first on the scalp, followed by the trunk, and then the extremities, with the highest concentration of lesions on the trunk (centripetal distribution). Lesions also can occur on mucous membranes of the oropharynx, respiratory tract, vagina, conjunctiva, and the cornea. Lesions are usually 1 to 4 mm in diameter. The vesicles are superficial and delicate, and contain clear fluid on an erythematous base. Vesicles may rupture or become purulent before they dry and crust. Successive crops appear over several days, with lesions present in several stages of development. For example, macular lesions may be observed in the same area of skin as mature vesicles. Healthy children usually have 200-500 lesions in 2 to 4 successive crops.

The **clinical course** in healthy children is generally mild, with malaise, pruritus (itching), and fever up to 102°F for 2 to 3 days. Adults may have more severe disease and have a higher incidence of complications. Respiratory and gastrointestinal symptoms are absent. Children with lymphoma and leukemia may develop a severe progressive form of varicella characterized by high fever, extensive vesicular eruption, and high complication rates. Children infected with human immunodeficiency virus may also have severe, prolonged illness.

Recovery from primary varicella infection usually results in lifetime immunity. In otherwise healthy persons, a second occurrence of chickenpox is uncommon, but may occur, 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

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

Herpes zoster, or shingles, occurs when latent VZV reactivates and causes recurrent disease. The immunologic mechanism that controls latency of VZV is not well understood. However, factors associated with recurrent disease include aging, immunosuppression, intrauterine exposure to VZV, and varicella at a young age (<18 months). In immunocompromised persons, zoster may disseminate, causing generalized skin lesions, and central nervous system, pulmonary, and hepatic involvement.

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

COMPLICATIONS

Acute varicella is generally mild and self-limited, but may be associated with complications. The most common complications of varicella include **secondary bacterial infections** of skin lesions, dehydration, pneumonia, and central nervous system involvement. Secondary bacterial infections of skin lesions with staphylococcus or streptococcus are the most common cause of hospitalization and outpatient medical visits. Secondary infection with invasive group A streptococci may cause serious illness and lead to hospitalization or death. **Pneumonia** following varicella is usually viral, but may be bacterial. Secondary bacterial pneumonia is more common in children <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.

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

In the prevaccine era, approximately 11,000 persons with varicella required hospitalization each year. Hospitalization rates were approximately 2-3 per 1,000 cases among healthy children and 8 per 1,000 cases among adults. Death occurred in approximately 1 in 60,000 cases. From 1990 through 1996, an average of 103 deaths from varicella was reported each year. Most deaths occur in immunologically normal children and adults.

The risk of complications from varicella varies with age. Complications are infrequent among healthy children. They are much higher in persons >15 years of age and infants <1 year of age. For instance, among children 1-14 years of age, the fatality rate of varicella is approximately 1 per 100,000 cases. Among persons 15-19 years, the fatality rate 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 account for approximately 35% of mortality.

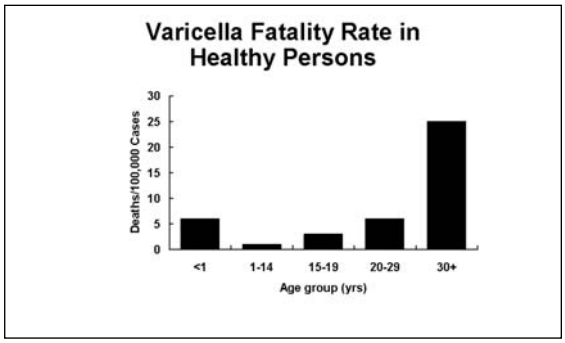
Immunocompromised persons have a high risk of serious varicella infection and a high risk of disseminated disease (up to 36% in one

Varicella Complications

- Bacterial infection of lesions
- CNS manifestations
- Pneumonia (rare in children)
- Hospitalization ~3 per 1000 cases
- Death ~ 1 per 60,000 cases

Groups at Increased Risk of Complications of Varicella

- Normal adults
- Immunocompromised persons
- Newborns with maternal rash onset within 5 days before to 48 hours after delivery



report). These persons may have multiple organ system involvement, and the disease may become fulminant and hemorrhagic. The most frequent complications in immunocompromised persons are pneumonia and encephalitis. Children with HIV infection are at increased risk for morbidity from varicella and herpes zoster.

PERINATAL INFECTION

The onset of maternal varicella from 5 days before to 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.

CONGENITAL VZV INFECTION

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

Congenital Varicella Syndrome

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

LABORATORY DIAGNOSIS

Laboratory diagnosis is not routinely required, but is useful if confirmation of the diagnosis or determination of susceptibility is necessary.

While rarely necessary for diagnosis, 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.

Varicella Laboratory Diagnosis

- Isolation of varicella virus from clinical specimen
- Rapid varicella virus identification using direct fluorescent antibody (DFA) testing
- Significant rise in varicella IgG by any standard serologic assay (e.g., enzyme immunoassay)

Rapid varicella zoster virus identification. Rapid virus identification techniques are indicated for a case with severe or unusual disease to initiate specific antiviral therapy. The **direct fluorescent antibody (DFA) test** is the method of choice for rapid clinical diagnosis. This test is sensitive, specific, and widely available. Results are available within several hours. 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. Other specimen sources such as nasopharyngeal secretions, saliva, blood, urine, bronchial washings,

and cerebrospinal fluid are considered less desirable sources than skin lesions since positive test results from such specimens are much less likely. Because viral proteins persist after cessation of viral replication, 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 compliment fixation (CF), indirect fluorescent antibody (IFA), fluorescent antibody to membrane antigen (FAMA), neutralization, indirect hemagglutination (IHA), immune adherence hemagglutination (IAHA), radioimmunoassay (RIA), latex agglutination (LA), and enzyme-linked immunosorbent assay (ELISA). Enzyme linked immunosorbent assay (ELISA) is sensitive and specific, simple to perform, and is widely available commercially. A commercially available latex agglutination (LA) is sensitive, and simple and rapid to perform. LA is generally more sensitive than commercial ELISA tests. 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 latex agglutination 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 the diagnosis of acute varicella infection, serologic confirmation would include a significant rise in varicella IgG by any standard serologic assay. Testing using commercial kits for IgM antibody is not recommended since available methods lack sensitivity and specificity; false positive IgM results are common in the presence of high IgG levels. The National VZV Laboratory at CDC has developed a reliable IgM capture assay. Call 404-639-0066, 404-639-3667, or email vzvlab@cdc.gov for details about collecting and submitting specimens for testing.

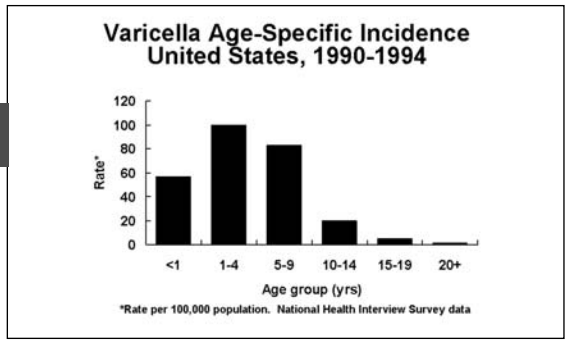
EPIDEMIOLOGY

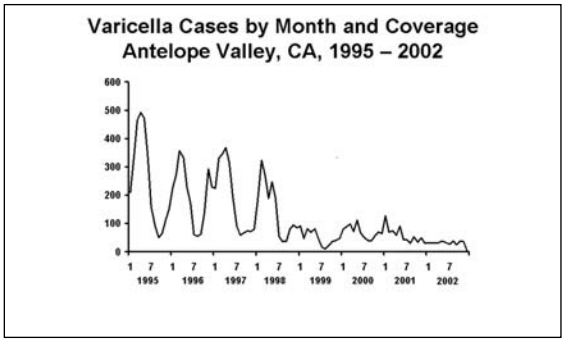
OCCURRENCE

Varicella and herpes zoster occur worldwide. There are data that suggest that varicella infection is less common in childhood in tropical areas, where chickenpox occurs more commonly among adults. The reason(s) for this difference in age distribution are not known with certainty, but may be due to lack of childhood varicella infection in rural populations.

Varicella Epidemiology

• Reservoir	Human
• Transmission	Airborne droplet Direct contact with lesions
• Temporal pattern	Peak in winter and early spring (U.S.)
• Communicability	1-2 days before to 4-5 days after onset of rash May be longer in immunocompromised





RESERVOIR

Varicella is a human disease. No animal or insect source or vector is known to exist.

TRANSMISSION

Infection with VZV occurs through the respiratory tract. The most common mode of transmission of VZV is believed to be person-to-person from infected respiratory tract secretions. Transmission may also occur by respiratory contact with airborne droplets, or by direct contact or inhalation of aerosols from vesicular fluid of skin lesions of acute varicella or zoster.

TEMPORAL PATTERN

In temperate areas, varicella has a distinct seasonal fluctuation, with the highest incidence occurring in winter and early spring. In the United States, incidence is highest between March and May, and lowest between September and November. Less seasonality is reported in tropical areas. Herpes zoster has no seasonal variation and occurs throughout the year.

COMMUNICABILITY

The period of communicability extends from 1 to 2 days before the onset of rash through the first 4 to 5 days, or until lesions have formed crusts. Immunocompromised patients with varicella are probably contagious during the entire period new lesions are appearing. The virus has not been isolated from crusted lesions.

Varicella is highly contagious. It is less contagious than measles, but more so than mumps and rubella. Secondary attack rates among susceptible household contacts of persons with varicella are as high as 90% (that is, 9 out 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 1991, but some states continued to report cases to CDC. Between 100,000 to 200,000 cases of varicella are reported annually.

In the prevaccine era, the majority of cases (approximately 85%) occurred among children less 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 account 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, have fallen significantly since licensure of vaccine in 1995. In 2001, varicella vaccination coverage among children 19-35 months in these areas was estimated to be 74%-84%. Compared with 1995, varicella cases declined 76%-86% in 2001. Cases declined most among children aged 1-4 years, but cases declined in all age groups including infants and adults, indicating reduced transmission of the virus in these communities.

Reduction of Reported Varicella by Age, Active Surveillance Sites, 1995 to 2001

Age	-------Surveillance Area------- Antelope Valley, CA	West Phila., PA	Travis County, TX
< 1 year	73%	87%	87%
1–4 years	88%	91%	87%
5–9 years	71%	80%	87%
10–14 years	51%	78%	89%
15–19 years	60%	85%	78%
≥20 years	77%	74%	54%
Overall	76%	86%	86%

*Travis County: 1995 vs 2000

HERPES ZOSTER

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

VARICELLA VACCINE

CHARACTERISTICS

Varicella zoster vaccine is a live attenuated viral vaccine, derived from the Oka strain of VZV. The vaccine virus was isolated by Takahashi in the early 1970s from vesicular fluid from a healthy child with varicella disease. Varicella vaccine was licensed for general use in Japan and Korea in 1988. It was licensed in the United States in 1995. The virus was attenuated by sequential passage in human embryonic lung cell culture, embryonic guinea pig fibroblasts, and in WI-38 human diploid cells. The Oka/Merck vaccine has undergone further passage through MRC-5 human diploid cell cultures for a total of 31 passages.

Varicella Vaccine

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

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

The reconstituted vaccine contains small amounts of sucrose, processed porcine gelatine, sodium chloride, monosodium L-glutamate, sodium diphosphate, potassium phosphate, and potassium chloride, and trace quantities of residual components of MRC-5 cells (DNA and protein), EDTA, neomycin, and fetal bovine serum. The vaccine does not contain egg, ovalbumin, or preservative.

IMMUNOGENICITY AND VACCINE EFFICACY

After one dose of vaccine, 97% of children 12 months to 12 years of age develop detectable antibody titers. Over 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 80%-90% against infection, and 85%-95% against moderate or severe disease.

Among healthy adolescents and adults, an average of 78% develop antibody after one dose and 99% develop antibody after a second dose given 4 to 8 weeks later. Antibody has persisted for at least 1

Breakthrough Infection

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

Breakthrough Infection

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

MMWR 2001;50(47):1058-61

Varicella Vaccine Recommendations Children

- Routine vaccination at 12 to 18 months of age
- Recommended for all susceptible children by the 13th birthday

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 longlasting, and is probably permanent in the majority of vaccinees. However, approximately 1% of vaccinees per year have developed breakthrough infections (*i.e.*, developed varicella disease even though they had responded to the vaccine). 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 the 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 also identified the presence of asthma and/or use of steroids, and earlier age (i.e., <15 months) as a risk factor for breakthrough varicella. However, because of the inconsistency of these data, ACIP has not changed it's recommendations for use of varicella vaccine (see below).

Breakthrough varicella infection could be a result of several factors, including interference of vaccine virus replication by circulating antibody, impotent vaccine due to storage or handling errors, or inaccurate recordkeeping. Interference from live viral vaccine administered before varicella vaccine could also reduce vaccine effectiveness. A study in two health maintenance organizations found that children who received varicella vaccine less than 30 days after MMR vaccination had a 2.5-fold increased risk of breakthrough varicella compared with those who received varicella vaccine before, simultaneous 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 <30 days prior to varicella vaccine.

VACCINATION SCHEDULE AND USE

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

Varicella vaccine is also recommended for all susceptible children 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 assure varicella immunity by this age, because after 13 years of age varicella disease is more severe, complications are more frequent, and two doses of vaccine are required.

Varicella vaccine should be administered subcutaneously. It has been shown to be safe and effective in healthy children when admin-

istered at the same time as measles-mumps-rubella (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) as all other childhood vaccines. The Advisory Committee on Immunization Practices (ACIP) strongly recommends that varicella vaccine be administered simultaneously with all other vaccines recommended at 12 to 18 months of age.

Children with a reliable history of chickenpox can be assumed to be immune to varicella. A parental history is acceptable, and physician documentation is not necessary. Children without a reliable history, or with an uncertain history of chickenpox should be considered susceptible. 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 susceptible. Prior history of chickenpox is not a contraindication to varicella vaccination.

Varicella vaccine should be administered to all **susceptible adolescents and adults.** Approximately 80% of adolescents and adults respond to a single dose of varicella vaccine. In contrast, at least 97% of healthy children will develop detectable antibody after a single dose. As a result, persons 13 years of age and older should receive **two doses** of varicella vaccine separated by 4 to 8 weeks. If there is a lapse of more than 8 weeks after the first dose, the second dose may be administered at any time without repeating the first dose.

Adolescents and adults with reliable parental or personal histories of chickenpox can be assumed to be immune. Those without a reliable history can be considered to be susceptible, or may be tested to determine varicella immunity. Epidemiologic and serologic studies indicate that up to 90% of adults are immune to varicella, including those who do not recall having had chickenpox. As a result, serologic testing prior to vaccination is likely to be cost effective for adults. As with children, a prior history of chickenpox is not a contraindication to varicella vaccination.

Assessment of varicella immunity of all adolescents and adults, and vaccination of those who are susceptible, is 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.

Varicella vaccination should be considered for **susceptible adolescents and adults who are at high risk of exposure to varicella.** This group includes persons who live or work in environments in which there is a high likelihood of transmission of varicella, such as teachers of young children, daycare workers, and residents and staff in institutional settings; persons who live or work in environments in

Varicella Vaccine Recommendations
Adolescents and Adults

- Persons ≥13 years of age without history of varicella
- Two doses separated by 4 - 8 weeks
- Up to 90% of adults immune
- Serologic testing may be cost effective

Varicella Vaccine Recommendations
Adolescents and Adults

- Susceptible persons at high risk of exposure or severe illness
  - Teachers of young children
  - Institutional settings
  - Military
  - Women of childbearing age
  - International travelers

Varicella Vaccine Recommendations
Adolescents and Adults

- Susceptible persons likely to expose persons at high-risk for severe illness
  - Healthcare workers
  - Family members of immunocompromised persons

which varicella transmission may occur (*e.g.* college students, inmates and staff of correctional institutions, and military personnel); nonpregnant women of childbearing age, in order to reduce the risk of VZV transmission to the fetus if the susceptible woman should develop varicella during pregnancy; and international travelers.

Vaccination of Healthcare Workers

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

Varicella vaccination is also recommended for susceptible **adolescents and adults who will have close contact with persons at high risk for serious complications of acquired varicella.** This group would include healthcare workers and susceptible family contacts of immunocompromised individuals.

The ACIP recommends that **all healthcare workers** be immune to varicella, either from a reliable history of varicella disease or vaccination. In healthcare settings, serologic screening of personnel who are uncertain of their varicella history, or who claim not to have had the disease, is likely to be cost effective. **Testing for varicella immunity following two doses of vaccine is not necessary** because 99% of persons are seropositive after the second dose.

Seroconversion may not always result in full protection against disease (see section on immunogenicity and vaccine efficacy for information on breakthrough infection). If a vaccinated healthcare worker is exposed to varicella, the exposed person should be tested for varicella antibody as soon as possible following the exposure. Persons with detectable antibody are unlikely to develop varicella. Persons without antibody can be retested 5-6 days later to determine if an anamnestic response is present (*i.e.*, antibody appears quickly after exposure). If antibody is present less than 7 days after exposure it is unlikely that the exposed person will develop disease. Persons who remain susceptible (*i.e.*, antibody negative) 7 days following exposure should be furloughed, or monitored very closely and then furloughed at the onset of symptoms suggestive of varicella.

The risk of transmission of vaccine virus from a vaccinated person to a susceptible contact appears to be very low (see Transmission of Varicella Vaccine Virus, below), and the benefits of vaccinating susceptible healthcare workers clearly outweigh this potential risk. Transmission of vaccine virus appears to occur primarily if and when the vaccinee develops a vaccine-associated rash. As a safeguard, institutions may wish to consider precautions for personnel who develop a rash following vaccination (*e.g.*, avoidance of contact with persons at high risk of serious complications, such as susceptible immunosuppressed persons).

Varicella Vaccine Postexposure Prophylaxis

- **Varicella vaccine is recommended for use in susceptible person after exposure to varicella**
  - **–70%-100% effective if given within 72 hours of exposure**
  - **–not effective if >5 days but will produce immunity if not infected**

POSTEXPOSURE PROPHYLAXIS

Data from the United States and Japan in a variety of settings indicate that varicella vaccine is effective in preventing illness or modifying the severity of illness if used within 3 days, and possibly up to 5 days, of exposure. ACIP recommends the vaccine for use in susceptible persons 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 susceptible health care workers 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. Varicella vaccine should be used for outbreak control by advising exposed susceptible persons to contact their healthcare providers for vaccination or by offering vaccination through the health department. Guidelines for varicella outbreak investigation and control are available from state health departments and from the National Immunization Program.

ADVERSE REACTIONS FOLLOWING VACCINATION

The most common adverse reactions following varicella vaccine are **injection site complaints** such as pain, soreness, redness, and swelling. Based on information from the manufacturer's clinical trials of varicella vaccine, local reactions are reported by 19% of children, and by 24% of adolescents and adults (33% following the second dose). These local adverse reactions are generally mild and self-limited. A varicella-like rash at injection site is reported by 3% of children, and by 1% of adolescents and adults following the second dose. In both circumstances, there has been a median of two lesions. These lesions generally occur within 2 weeks, and are most commonly maculopapular rather than vesicular.

A generalized varicella-like **rash** is reported by 4% to 6% of recipients of varicella vaccine (1% after the second dose in adolescents and adults), with a median of five lesions. Most of these generalized rashes occur within 3 weeks and most are maculopapular.

Fever within 42 days of vaccination is reported by 15% of children and 10% of adolescents and adults. The majority of these episodes of fever have been attributed to intercurrent illness rather than to the vaccine.

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

Varicella Vaccine Adverse Reactions

- Injection site complaints - 20%
- Rash - 4% - 6%
  - May be maculopapular rather than vesicular
  - Average 5 lesions
- Systemic reactions uncommon

Zoster Following Vaccination

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

CONTRAINDICATIONS AND PRECAUTIONS TO VACCINATION

Varicella Vaccine
Contraindications and Precautions

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

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

Persons with **immunosuppression** due to leukemia, lymphoma, generalized malignancy, immune deficiency disease, or immunosuppressive therapy should not be vaccinated. However, treatment with low dose (<2 mg/kg/day), alternate day, topical, replacement, or aerosolized steroid preparations is not a contraindication to varicella vaccination. Persons whose immunosuppressive therapy with steroids has been stopped for 1 month (3 months for chemotherapy) may be vaccinated. Varicella vaccine is available from the manufacturer through a research protocol for special use in certain patients with acute lymphoblastic leukemia in remission. Please consult the ACIP statement or contact the manufacturer for further information.

Varicella Vaccine
Use in Immunocompromised Persons

- Most immunocompromised persons should not be vaccinated
- Vaccinate persons with isolated humoral immunodeficiency
- Consider varicella vaccination for asymptomatic HIV-infected children with CD4% >25% (CDC class A1 and N1)

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

Persons with moderate or severe cellular immunodeficiency resulting from infection with human immunodeficiency virus (HIV), including persons diagnosed with acquired immune deficiency syndrome (AIDS) should not receive varicella vaccine. However, vaccination should be considered for children with asymptomatic or mildly symptomatic HIV infection (CDC class N1 or A1, age-specific CD4+ T-lymphocyte percentage of $\geq$25%). These children should receive two doses of varicella vaccine with a 3 month interval between doses. Because persons with impaired cellular immunity are potentially at greater risk for complications after vaccination with a live vaccine, these vaccinees should be encouraged to return for evaluation if they experience a postvaccination varicella-like rash.

Women known to be **pregnant** or attempting to become pregnant should not receive varicella vaccine. The effects of varicella vaccine on a developing fetus are unknown. Since infection with wild varicella virus poses only a small risk to the fetus, and the vaccine virus is attenuated, the risk to the fetus, if any, should be even lower. Although the manufacturer's package insert states otherwise, ACIP and the American Academy of Pediatrics recommend that pregnancy be avoided for 1 month following receipt of varicella vaccine.

The manufacturer, in collaboration with the Centers for Disease Control and Prevention 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, intravenous immune globulin, varicella zoster immune globulin [VZIG]) on the response to varicella vaccine virus is unknown. Because of the potential inhibition of the response to varicella vaccination by passively transferred antibodies, varicella vaccine should not be administered for 3-11 months after antibody-containing blood products. ACIP recommends applying the same intervals used to separate antibody-containing products and MMR to varicella vaccine (see the chapter on General Recommendations on Immunization for additional details). Immune globulin or VZIG should not be given for 3 weeks following vaccination unless the benefits exceed those of the vaccine. In such cases, the vaccinees should either be revaccinated or tested for immunity ≥3 months later (depending on the antibody-containing product administered) and revaccinated if seronegative.

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

TRANSMISSION OF VARICELLA VACCINE VIRUS

Available data suggest that transmission of vaccine virus is a rare event. Instances of suspected secondary transmission of vaccine virus have been reported. However, in few instances has the secondary clinical illness been shown to be caused by vaccine virus. Several cases of suspected secondary transmission have been determined to have been caused by wild varicella virus. However, in studies of household contacts, several instances of asymptomatic seroconversion have been observed. It appears that transmission occurs mainly, and perhaps only, when the vaccinee develops a rash. If a vaccinated child develops a rash, it is recommended that close contact with susceptible persons at high-risk of complications of varicella, such as immunocompromised persons, be avoided until

Transmission of Varicella Vaccine Virus

- Transmission of vaccine virus uncommon
- Asymptomatic seroconversion may occur in susceptible contacts
- Risk of transmission increased if vaccinee develops rash

the rash has resolved.

VACCINE STORAGE AND HANDLING

Vaccine Storage and Handling

- Store frozen at -15 C (+5 F) or lower
- Generally should not be refrozen
- Store diluent at room temperature or refrigerate
- Discard if not used within 30 minutes of reconstitution

Varicella vaccine is very fragile and must be handled with extreme care. To maintain potency, the lyophilized vaccine must be stored frozen at an average temperature of +5°F (-15°C). Household freezers, including frost-free models, manufactured within the last 5-10 years, are designed to maintain temperatures as low as -4°F (-20°C), and are acceptable for storage of the vaccine. Refrigerators with ice compartments that are not tightly enclosed or are enclosed with unsealed, uninsulated doors (*i.e.*, small dormitory-style refrigerator/freezer combinations) are not be 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, which does not contain preservative or other antiviral substances that might inactivate the vaccine virus. Once reconstituted, the vaccine must be used immediately to minimize loss of potency. The vaccine must be discarded if not used within 30 minutes of reconstitution.

Varicella Vaccine Information
800-9VARIVAX

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

Because of the lability of varicella vaccine, transport of the vaccine from a central clinic or storage area to an off-site clinic can be difficult. If off-site transport is attempted, a high-quality container should be used, the vaccine should be transported on dry ice, and the temperature should be monitored continuously, to assure that the appropriate storage temperature is maintained. The vaccine may be kept at refrigerator temperature for up to 72 hours, but must then be discarded if not used. The vaccine should not be refrozen.

Varicella Zoster Immune Globulin (VZIG)

- May modify or prevent disease if given <96 hours after exposure
- Indications
  - immunocompromised persons
  - newborn of mothers with onset 5 days before to 2 days after birth
  - premature infants with postnatal exposure
  - susceptible adults and pregnant women

VARICELLA ZOSTER IMMUNE GLOBULIN (VZIG)

VZIG is a human blood product that contains high titers of varicella zoster virus antibody. It was licensed in 1981, and is **available**

from the distributor (FFF Enterprises, Inc., Temecula, CA) by calling 800-843-7477. If administered within 96 hours of exposure, VZIG can modify or prevent clinical varicella and prevent complications or death, especially in susceptible immunocompromised individuals.

The decision to administer VZIG should be based on whether the patient is susceptible either by having a negative history of chickenpox or by lacking documentation of vaccination, whether the exposure is likely to result in infection and, most importantly, whether the patient is at greater risk of complications than the general population. VZIG is expensive ($400-$500 for the maximum dose in an adult) and provides only temporary protection.

VZIG is indicated for use in susceptible individuals at high risk for complications who have had a significant exposure (continuous household contact; playmate contact of more than an hour; hospital contact in the same 2- to 4-bed room; or prolonged direct contact) to a person with varicella. It is most commonly used for postexposure prophylaxis of immunocompromised children (immune deficiencies, neoplastic disease, or on immunosuppressive therapy), and newborns of mothers with varicella onset 5 days before to 48 hours after delivery. It is also recommended for premature infants with postnatal exposure, including those born at less than 28 weeks gestation or less than 1,000 gram birth weight (who may not have received adequate maternal antibody regardless of whether the mother is immune), or premature infants whose mother is not immune to varicella.

Healthy and immunocompromised adults and pregnant women are at increased risk of complications of varicella. VZIG should be considered if such individuals are susceptible. There is no evidence that VZIG will prevent congenital varicella if given as postexposure prophylaxis to a pregnant woman.

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

More detailed information on the evaluation of a person exposed to varicella and the use of VZIG may be found in the varicella ACIP statement.

SPECIAL VARICELLA EXPOSURE SITUATIONS

HOSPITAL PERSONNEL

Susceptible workers with significant exposure to varicella should be

relieved from direct patient contact from day 10 to day 21 after exposure. If workers develop chickenpox, varicella lesions must be crusted before they return to direct patient contact. Receipt of VZIG does not change this recommendation for reassignment. Since VZIG can prolong the incubation period, the period of removal from direct patient contact should be lengthened by 1 week or more.

NEWBORNS

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

ANTIVIRAL THERAPY

Varicella Antiviral Therapy

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

2003 AAP Red Book

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

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

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

SELECTED REFERENCES

American Academy of Pediatrics. Varicella zoster infections. In: Pickering L, ed. *Red Book: 2003 Report of the Committee on Infectious Diseases*. 26th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2003:672-86.

Asano Y, Suga S, Yoshikawa T, et al. Experience and reason: twenty year follow-up of protective immunity of the Oka strain live varicella vaccine. *Pediatrics* 1994;94:524-6.

CDC. Prevention of varicella. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 1996;45(RR-11):1-36.

CDC. Prevention of varicella. Update recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 1999;48:1-5.

CDC. Simultaneous administration of varicella vaccine and other recommended childhood vaccines - United States, 1995-1999. *MMWR* 2001;50:1058-61.

Gershon AA, Takahashi M, Seward J. Varicella vaccine. In: Plotkin SA, Orenstein WA, eds. *Vaccines*. 4th ed. Philadelphia: Saunders; 2004:783-823.

Seward JF, Watson BM, Peterson CL, et al. Varicella disease after introduction of varicella vaccine in the United States, 1995-2000. *J Am Med Assoc* 2002;287:606-11.

Shields KE, Galil K, Seward J, et al. Varicella vaccine exposure during pregnancy: data from the first 5 years of the pregnancy registry. *Obstet Gynecol* 2001; 98:14-9

Vazquez M, LaRuissa PS, Gershon AA, et al. The effectiveness of the varicella vaccine in clinical practice. *N Eng J Med* 2001;344:955-60.

Weller TH. Varicella–herpes zoster virus. In: Evans AS, Kaslow RA, eds. *Viral Infections of Humans. Epidemiology and Control*. 4th ed. New York, NY: Plenum Medical Book Company; 1997:865-92.

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 differentiated epidemiologically from long-incubation period hepatitis B in the 1940s. The development of serologic tests allowed definitive diagnosis of hepatitis B. Identification of the virus, and development of serologic tests in the 1970s 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
- Most commonly reported type of hepatitis in the United States

Hepatitis A is the most common type of hepatitis reported in the United States. Until recently, the primary methods used for preventing hepatitis A have been hygienic measures and passive immunization with immune globulin (IG) to provide short-term protection. Hepatitis A vaccines were licensed in 1995 and 1996 for use in persons ≥2 years of age, and can 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, eradicate 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 may be experimentally infected. 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), formalin, and chlorine.

Hepatitis A Virus

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

PATHOGENESIS

HAV is acquired by mouth (fecal-oral) 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 7-10 days after onset of symptoms. Most infected people 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

CLINICAL FEATURES

The **incubation period** of hepatitis A is 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 signs and symptoms that include fever, malaise, anorexia, nausea, abdominal discomfort, dark urine and jaundice. Clinical illness usually does not last longer than 2

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

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. Among children <6 years of age, most (70%) infections are asymptomatic. Among older children and adults, infection is usually symptomatic with jaundice occurring in >70% of patients. HAV infection occasionally produces fulminant hepatitis A.

COMPLICATIONS

Fulminant hepatitis A causes about 100 deaths per year in the U.S. The case-fatality rate among reported cases of all ages is approximately 0.3%, but can be higher among older persons (approximately 2% among persons >40 years of age).

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 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 >$200 million.

LABORATORY DIAGNOSIS

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

Anti-HAV IgG antibody appears in the convalescent phase of infection, remains present in serum for the lifetime of the person and confers enduring protection against disease. The antibody test for total anti-HAV measures both anti-HAV IgG and anti-HAV IgM. Persons who are total anti-HAV positive and anti-HAV IgM negative have serologic markers indicating immunity consistent with either past infection or vaccination.

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

MEDICAL MANAGEMENT

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

EPIDEMIOLOGY

OCCURRENCE

Hepatitis A occurs throughout the world. Some areas are highly endemic, 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 of illness, when HAV concentration in stool is highest. The risk then decreases and is minimal the week after the onset of jaundice.

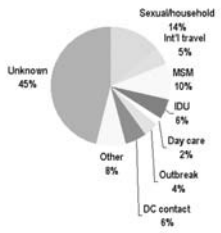
RISK FACTORS

From 1990 through 2000, the most frequently reported source of infection was personal contact (household or sexual) with an infected person (14%). Two percent of cases involved a child or employee in daycare; 6% of cases were a contact of a child or employee in daycare; 5% of cases reported recent international travel; and 4% of cases reported being part of a recognized food-borne 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 cases could not identify a risk factor for their infection.

Hepatitis A Epidemiology

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

Hepatitis A – United States, 1990-2000
Risk Factors



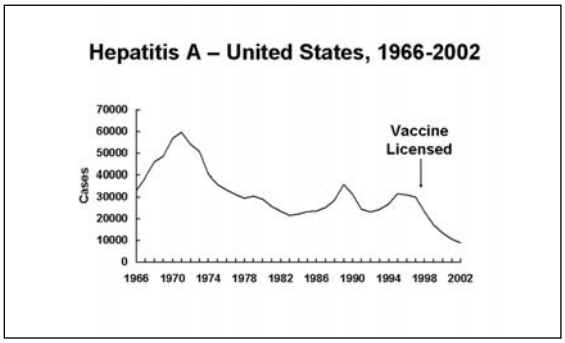
Groups at increased risk of hepatitis A or its complications include international travelers, men who have sex with men, and illegal drug users. Outbreaks of hepatitis A have also been reported among person working with hepatitis A-infected primates. This is the only occupational group known to be at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

Persons with chronic liver disease are not at increased risk of infection, but are at increased risk of 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.

Food handlers 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. Health-care 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 U.S., 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.

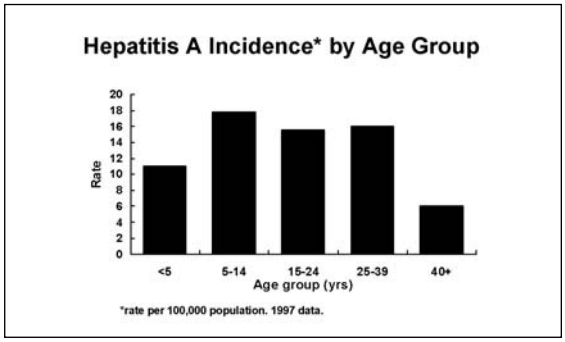
SECULAR TRENDS IN THE UNITED STATES



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. In 2002, a total of 10,609 cases of hepatitis A were reported. After adjusting for under-reporting, 93,000 infections are estimated to have occurred in 2002, 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. From 1987 through 1997, the average annual incidence of reported hepatitis A in the U.S. was approximately 10 cases per 100,000 population.

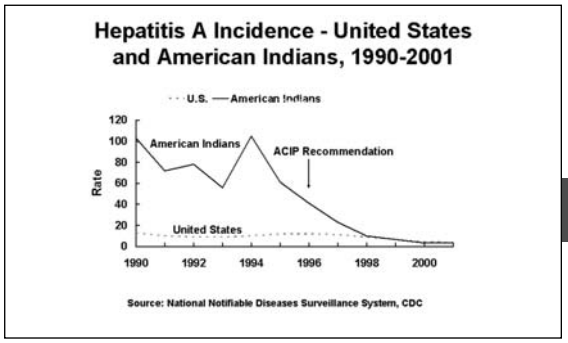
The highest rates of hepatitis A are among children 5-14

years of age (15-22 cases per 100,000 population in 1987-1997). Approximately one third of reported cases occur among children <15 years of age.



Based on testing from phase 1 of the Third National Health and Nutrition Examination Survey (NHANES III) conducted in 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 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.

During the past several decades, the incidence of reported hepatitis A has been substantially higher in the western United States than in other parts of the country. From 1987-1997, 11 mostly western states (AZ, AK, OR, NM, UT, WA, OK, SD, ID, NV, CA) accounted for 50% of all reported cases but only 22% of the U.S. population.



Many hepatitis A cases in the United States occur in the context of community-wide epidemics. Communities which 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) and few cases among persons >15 years of age. These communities often are relatively well-defined either geographically or ethnically and include Native American, Alaskan Native, Pacific Islander, 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.

In **intermediate-rate communities**, hepatitis A cases occur primarily among children, adolescents, and young adults. Epidemics often occur at regular intervals and persist for several years with rates typically between 50 and 200 cases per 100,000 per year. However, some communities experience sustained elevated rates. Often cases are concentrated in specific census tracts or neighborhoods within a larger community. In these communities, children with asymptomatic HAV infection can be a substantial source of infection for older persons during community-wide outbreaks.

CASE DEFINITION

The case definition for hepatitis A was approved by the Council of State and Territorial Epidemiologists (CSTE) in 1997. It reflects a

clinical diagnosis of hepatitis and, because HAV cannot be differentiated from other types of viral hepatitis on clinical or epidemiologic features alone, serologic evidence of HAV-specific IgM antibody is necessary.

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

HEPATITIS A VACCINE

CHARACTERISTICS

Hepatitis A Vaccines

- Inactivated whole virus
- Pediatric and adult formulations
- Licensed for persons ≥2 years

Two inactivated whole virus hepatitis A vaccines is available: Havrix (GlaxoSmithKline) and VAQTA (Merck Vaccine Division). 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. **Neither vaccine is currently licensed for children <2 years of age.**

IMMUNOGENICITY AND VACCINE EFFICACY

Hepatitis A Vaccine Immunogenicity

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

Children (≥2 years) 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 percent will seroconvert within a month. 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 2 doses.

Hepatitis A Vaccine Efficacy

GlaxoSmithKline
- 40,000 Thai children 1-16 years
- Vaccine efficacy 94%

Merck
- 1,000 children 2-16 years
- Vaccine efficacy 100%

Both vaccines are highly effective in the prevention of 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 2 doses one 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 1 dose while living in a community with a high HAV disease rate.

Data concerning the long-term persistence of antibody and of immune memory are limited because the currently available vaccines have been being evaluated for <10 years. Estimates of antibody persistence derived from kinetic models of antibody decline indicate that protective levels of anti-HAV could be present for ≥20 years. 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

Since its introduction in 1995, hepatitis A vaccine has been prima-

rily targeted to individuals at increased risk of 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 in 1999 recommended **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 cases per 100,000 population or more but less than 20 cases per 100,000 population.**

Determination of age groups recommended for vaccination should take into account community disease patterns. In communities with high rates of hepatitis A, routine vaccination of children beginning at 2 years of age and older and catch-up vaccination of preschool children should receive the highest priority. In other areas where routine childhood vaccination is recommended, possible strategies include vaccination one or more single age cohorts of children or adolescents (*e.g.*, at entry into preschool, elementary school and/or middle school), vaccination of children and adolescents in selected settings (*e.g.*, daycare) or vaccination of children and adolescents with a wide range of ages in a variety of settings, such as when they seek healthcare for other purposes.

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

Havrix is available in 2 formulations - pediatric (720 EL.U. per 0.5 mL dose) and adult (1,440 EL.U. per 1.0 mL dose). Children 2-18 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 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

Recommended Doses of Havrix® Hepatitis A Vaccine

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

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

length appropriate for the vaccinee's age and size (minimum of 1 inch) should be used. VAQTA is quantified in units (U) of antigen

Hepatitis A Vaccine Recommendations

Routine hepatitis A vaccination should be considered for:

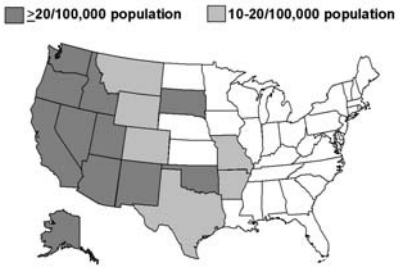
- Children >2 years in states, counties, or communities where the average annual hepatitis A rate during 1987-1997 was 10 to 20 per 100,000 population

Hepatitis A Vaccine Recommendations

Routine hepatitis A vaccination is recommended for:

- Children >2 years in states, counties, or communities where the average annual hepatitis A rate during 1987-1997 was ≥20 per 100,000 population

Hepatitis A – High Incidence States



and is available in a pediatric and adult formulation. Children 2-18 years of age should receive one dose of pediatric formulation (25 U per dose) with a booster dose 6-12 months later. Adults 19 years of age and older should receive one dose of adult formulation (50 U per dose) with a booster dose 6-12 months after the first dose. The vaccine should be administered intramuscularly into the deltoid muscle. A needle length appropriate for the vaccinee's age and size should be used (minimum of 1 inch).

Recommended Doses of VAQTA® Hepatitis A Vaccine

Group	Age	Dose (U)	Volume	No. Doses	Schedule*
Children and Adolescents	2-18 years	25	0.5 mL	2	0, 6-18
Adults	>18 years	50	1.0 mL	2	0, 6-12

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

Limited data indicate that vaccines from different manufacturers are 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 child 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 six calendar months. If the interval between the first and booster doses of hepatitis A vaccine is longer than the recommended interval of 6-18 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

Twinrix

- **Combination hepatitis B (adult dose) and hepatitis A vaccine (pediatric dose)**
- **Schedule: 0, 1, 6-12 months**
- **Approved for persons ≥18 years**

In 2001, the U.S. 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 3 dose series at 0, 1, and 6-12 months. Appropriate spacing of the doses must be maintained to assure long-term protection from both vaccines. The first and third doses of Twinrix should be separated by at least 6 months. The first and second doses should be separated by at least 4 weeks, and the second and third doses should be separated by at least 5 months. It is not necessary to restart the series

or add doses if the interval between doses is longer than the recommended interval. Twinrix is approved for persons aged 18 years and older, and can be used in persons in this age group with indications for both hepatitis A and hepatitis B vaccines.

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

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 2 years of age and older who are **traveling to or working in countries with high- or intermediate-risk of hepatitis A virus infection.** These areas include all areas of the world except Canada, Western Europe and Scandinavia, Japan, New Zealand, and Australia. Vaccinated persons can be assumed to be protected by 4 weeks after receiving the first dose, although the second dose 6 to 12 months later is necessary for long-term protection.

Available data suggest that 40%-45% of vaccinated persons might lack neutralizing antibody at 14 days after receiving the first dose. No data are currently available regarding the risk of hepatitis A among persons vaccinated 2-4 weeks before departure. Because protection might not be complete until 4 weeks after vaccination, persons traveling to a high-risk area less than 4 weeks after the initial dose should also be administered immune globulin (0.02 mL/kg) at a different anatomic injection site. Hepatitis A vaccine is not approved for children less than 2 years of age. Children <2 years of age should receive immune globulin (0.02-0.06 mL/kg, depending on length of stay) prior to travel to high-risk areas. Other groups which should be offered vaccine include **men who have sex with other men, drug users, 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 of fulminant hepatitis A should they become infected. **Susceptible persons who have chronic liver disease should be vaccinated.** Available data do not indicate a need for routine vaccination of persons with chronic hepatitis B virus or hepatitis C virus infections without evidence of chronic liver disease. 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**

Hepatitis A Vaccine Recommendations

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

Hepatitis A Vaccine Recommendations

- International travelers
- Men who have sex with men
- Drug users
- Persons with occupational risk
- Persons with chronic liver disease, including hepatitis C

Hepatitis A Vaccine Recommendations

- Healthcare workers: not routinely recommended
- Daycare centers: not routinely recommended
- Food handlers: may be considered based on local circumstances

Hepatitis A Serologic Testing

Prevaccination
- Not indicated for children
- May be considered for some adults and older adolescents

Postvaccination
- Not indicated

Hepatitis A Vaccine Adverse Reactions

- Pain at injection site
- Systemic reactions uncommon
- No serious adverse events reported

daycare centers, or persons who work in liquid or solid waste management (*e.g.*, sewer workers or plumbers). These groups have not been shown to be at increased risk of hepatitis A infection. **ACIP does not recommend routine hepatitis A vaccination for food service workers,** but vaccination may be considered based on local epidemiology.

PREVACCINATION SEROLOGIC TESTING

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

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

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

POSTVACCINATION SEROLOGIC TESTING

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

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 in 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 in <10% of recipients. No serious adverse reactions have been reported.

CONTRAINDICATIONS AND PRECAUTIONS TO VACCINATION

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

or following a prior dose of hepatitis A vaccine, hypersensitivity to alum or, in the case of Havrix, to the preservative 2-phenoxyethanol. Vaccination of persons with **moderate or severe acute illnesses** should be deferred until the patient 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.

Hepatitis A Vaccine Contraindications and Precautions

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

VACCINE STORAGE AND HANDLING

Hepatitis A vaccine should be stored and shipped at temperatures ranging from 35.6°F (2°C) to 46.4°F (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 U.S., 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. The IG is made with a serial ethanol precipitation procedure that has been shown to inactivate hepatitis B virus (HBV) and human immunodeficiency virus.

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

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

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

Recipients may include 1) persons with close contact (household or sexual) to a person with hepatitis A; 2) staff and attendees at child care centers where a hepatitis A case has been recognized; and 3) persons in certain common-source exposure situations (*e.g.*, to patrons of a food establishment with an HAV-infected food han-

dler, 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 a HAV exposure do not need IG.

IG can interfere with the response to live injected vaccines (*e.g.*, measles, mumps, rubella, and varicella vaccines). Thus, administration of live vaccines should be delayed for at least 3 months after administration of IG (see the chapter on General Recommendations on Immunization, p. 7). Conversely, unless the benefits of IG prophylaxis exceed the benefits of vaccination, IG should not be administered for 2 weeks after measles-, mumps-, and rubella-containing vaccines, and for 3 weeks after vaccination with varicella vaccine. If IG is given during this period, the person should be revaccinated with the live vaccine, but not sooner than 3 months after administration of IG.

DISEASE SURVEILLANCE AND REPORTING

Hepatitis A is a reportable disease in all states. Disease surveillance should be used to 1) monitor disease incidence in all age groups; 2) determine the epidemiologic characteristics of infected persons, including the source of their infection; 3) identify contacts of cases who require postexposure prophylaxis; 4) detect outbreaks; 5) determine the effectiveness of hepatitis A vaccination; and 6) determine missed opportunities for vaccination. Surveillance for hepatitis A is especially important because determining vaccination strategies to control ongoing outbreaks depends upon the identification of specific groups (*e.g.*, by geographic area, age group, or other characteristics) at increased risk of hepatitis A.

In the United States, case reports of viral hepatitis are classified as hepatitis A, hepatitis B, or hepatitis C/non-A, non-B hepatitis. Serologic testing is necessary to determine the etiology of viral hepatitis. Case reports should be based on laboratory confirmation (see Laboratory Diagnosis section). Each state and territory has regulations and/or laws governing the reporting of diseases and conditions of public health importance. These regulations/laws list the diseases and conditions that are to be reported and describe those persons or groups who are responsible for reporting, such as healthcare providers, hospitals, laboratories, schools, daycare facilities, and other institutions. Contact your state health department for reporting requirements in your state.

SELECTED REFERENCES

American Academy of Pediatrics. Measles. In: Pickering L ed. *Red Book: 2003 Report of the Committee on Infectious Diseases*. 26th ed. Elk Grove Village, IL: American Academy of Pediatrics, 2003:309-18.

Bell BP, Feinstone SM. Hepatitis A Vaccine. In: Plotkin SA, Orenstein, WA, eds. *Vaccines*. 4th ed. Philadelphia: Saunders Company; 2003:269-97.

CDC. Prevention of hepatitis A through active or passive immunization. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 1999;48(RR-12):1-37.

CDC. Hepatitis A vaccination of men who have sex with men - Atlanta, Georgia, 1996-1997. *MMWR* 1998;47:708-11.

CDC. Immunization of health-care workers. Recommendations of the Advisory Committee on Immunization Practices (ACIP) and the Hospital Infection Control Practices Advisory Committee (HICPAC). *MMWR* 1997;46(RR-18):1-42.

CDC. Hepatitis A vaccination programs in communities with high rates of hepatitis A. *MMWR* 1997;46;600-603.

CDC. Hepatitis A outbreak associated with green onions at a restaurant - Monaca, Pennsylvania, 2003. *MMWR* 1997;46:288-295.

Margolis HS, Alter MJ, Hadler SC. In: Evans AS, ed. *Viral Infections of Humans. Epidemiology and Control*. 3rd ed. New York, NY: Plenum Medical Book Company; 1998:363-418.

Peter G, ed. *1997 Red Book: Report of the Committee on Infectious Diseases*. 24th ed. Elk Grove Village, IL: American Academy of Pediatrics, 1997.

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, 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 this 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 among 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 the prevention of HBV infection.

Hepatitis B

- Epidemic jaundice described by Hippocrates in 5th century BC
- Jaundice reported among recipients of human serum and yellow fever vaccines in 1930s and 1940s
- Australian 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 a laboratory conditions. HBV is relatively resilient and, in some instances, has been shown to remain infectious on environmental surfaces for at least a month at room temperature.

Hepatitis B Virus

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

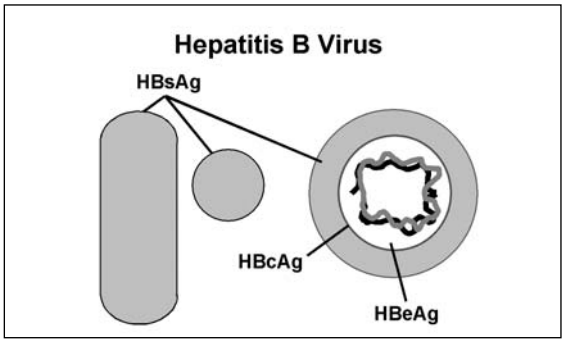
HBV is the most common known cause of chronic viremia, with an estimated 200 to 300 million chronic carriers worldwide. HBV infection is an established cause of acute and chronic hepatitis and cirrhosis. It is the cause of up to 80% of hepatocellular carcinomas, and is second only to tobacco among known human carcinogens. More than 250,000 persons die worldwide each year of hepatitis B-associated acute and chronic liver disease.

Hepatitis B Virus Infection

- $\geq$200 million carriers worldwide
- Established cause of chronic hepatitis and cirrhosis
- Human carcinogen - cause of up to 80% of hepatocellular carcinomas

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 great excess.



HBcAg is the nucleocapsid protein core of HBV. HBcAg is not detectable in serum by conventional techniques, but can be detected in liver tissue in 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 HBsAb antibody indicates immunity to HBV. **Antibody to HBcAg (Anti-HBc)** indicates infection with HBV at an undefined time in the past. **IgM class antibody to HBcAg (IgM anti-HBc)** indicates recent infection with HBV. **Antibody to HBeAg (Anti-HBe)** becomes detectable when HBeAg is lost and is associated with low infectivity of serum.

CLINICAL FEATURES

Hepatitis B Clinical Features

- Incubation period 6 weeks to 6 months
- Nonspecific prodrome of fever, malaise, headache, myalgia
- Illness not specific for hepatitis B
- At least 50% of infections asymptomatic

The clinical course of acute hepatitis B is indistinguishable from that of other types of acute viral hepatitis. The **incubation period** ranges from 6 weeks to 6 months (average, 120 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, myalgias, skin rashes, arthralgias 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, 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 from future infection.

Hepatitis B Complications

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

COMPLICATIONS

While most acute HBV infections in adults result in complete recovery, **fulminant hepatitis** occurs in about 1% to 2% of persons, with mortality rates of 63% to 93%. About 200 to 300 Americans die of fulminant disease each year. Although the consequences of acute HBV infection can be severe, most of the serious complica-

tions associated with HBV infection are due to chronic infection.

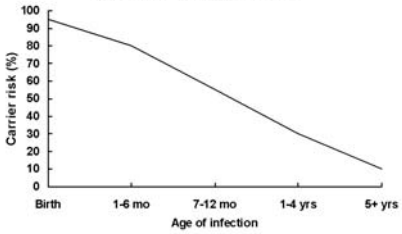
CHRONIC HBV INFECTION

Approximately 10% of all acute HBV infections progress to chronic infection, with the risk of chronic HBV infection decreasing with age. As many as 90% of infants who acquire HBV infection from their mothers at birth become carriers. Of children who become infected with HBV between 1 year and 5 years of age, 30% to 50% become carriers. By adulthood, the risk of becoming a carrier is 6% to 10%.

Persons with chronic infection are often asymptomatic and may not be aware that they are infected, yet are capable of infecting others. Chronic infection is responsible for most HBV-related morbidity and mortality, including **chronic hepatitis, cirrhosis, liver failure, and hepatocellular carcinoma.** 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 die each year in the United States of hepatitis B-related liver cancer.

Chronic Hepatitis B Virus Infection

- Chronic viremia
- Responsible for most mortality
- Overall risk 10%
- Higher risk with early 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 anti-HBc anti-HBs	Negative Negative Negative	Susceptible
HBsAg anti-HBc anti-HBs	Negative Negative Positive with ≥10mIU/mL*	Immune due to vaccination
HBsAg anti-HBc anti-HBs	Negative Positive Positive	Immune due to natural infection
HBsAg anti-HBc IgM anti-HBc anti-HBs	Positive Positive Positive Negative	Acutely infected
HBsAg anti-HBc IgM anti-HBc anti-HBs	Positive Positive Negative Negative	Chronically infected
HBsAg anti-HBc anti-HBs	Negative Positive Negative	Four interpretations possible†

*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 from reinfection. Anti-HBs can also be acquired as an immune response to hepatitis B vaccine or passively transferred by administration of HBIG. Using radioimmunoassay (RIA), a minimum of 10 sample ratio units should be used to designate immunity. Using 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 HBV infections and carriers 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 may be infected experimentally, HBV infection affects only humans. No animal or insect hosts or vectors are known to exist.

TRANSMISSION

The virus is transmitted by **parenteral or mucosal exposure to HBsAg-positive body fluids** from persons who are carriers or have acute 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 among homosexual men occurs 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 needle-sticks 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 in 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 when contaminated with infective blood or serum. Transfer of infective material to skin lesions or mucous membranes via inanimate environmental surfaces may occur by touching surfaces of various types of hospital equipment. Contamination of mucosal surfaces with infective secretions other than serum or plasma could occur with contact involving semen.

Perinatal transmission from mother to infant at birth is very efficient. If the mother is positive for both HBsAg and HBeAg, 70%-90% of infants will become infected in the absence of postexposure prophylaxis. The risk of perinatal transmission is about 20% if the mother is positive only for HBsAg. Up to 90% of these infected infants will become HBV carriers. An estimated 15%-25% of these carriers will ultimately die of liver failure secondary to chronic active hepatitis, cirrhosis, or primary hepatocellular carcinoma.

Hepatitis B Epidemiology

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

Hepatitis B Perinatal Transmission*

- If mother positive for HBsAg and HBeAg
  - 70%-90% of infants infected
  - 90% of infected infants become chronic carriers
- If positive for HBsAg only
  - 20% of infants infected
  - 90% of infected infants become chronic carriers

*in the absence of postexposure prophylaxis

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% 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 (<2% of the population is HBsAg-positive).

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

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 >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 in 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 <20% in low prevalence areas.

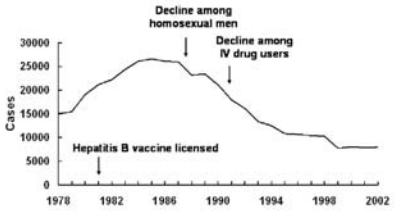
COMMUNICABILITY

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 the blood and body fluids of infected persons for 1 to 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.

Hepatitis B – United States, 1978-2002



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. In 1999, a provisional total of 6,495 cases were reported. The decline in cases during the 1980s and early 1990s is generally attributed to reduction of transmission among homosexual men and injection drug users as a result of HIV prevention.

HBV Disease Burden in the United States*

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

*2001 estimates

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 perinatal transmission account for approximately 4% each. Perinatal transmission accounted for a disproportionate 24% of chronic infections.

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

Although HBV infection is uncommon among adults in the general population (the lifetime risk of infection is <20%), it is highly prevalent in certain groups. Risk for infection varies with occupation, lifestyle, or environment (see next 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.

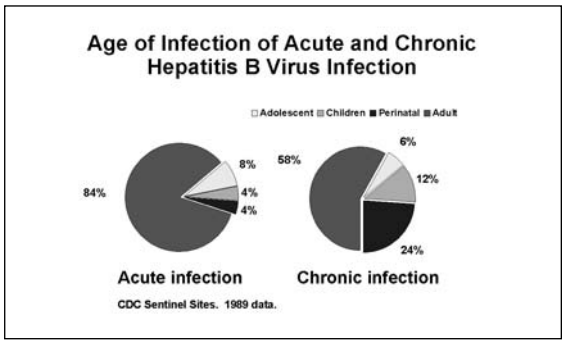
Prevalence of Hepatitis B in Various Population Groups

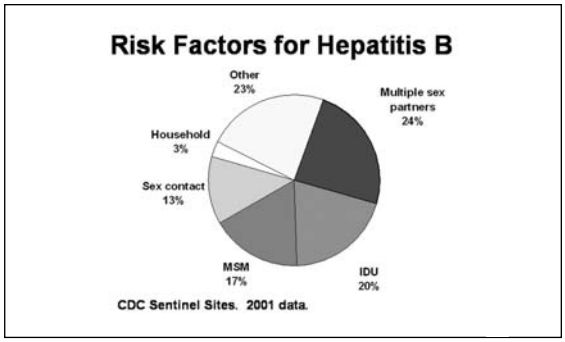
	Population Group	Prevalence of Serologic Markers of HBV Infection	
		HBsAg (%)	All Markers (%)
High-Risk	Immigrants/refugees from areas of high HBV endemicity.	13	70-85
	Clients in institutions for the developmentally disabled.	10-20	35-80
	Users of illicit parenteral drugs.	7	60-80
	Homosexually active 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

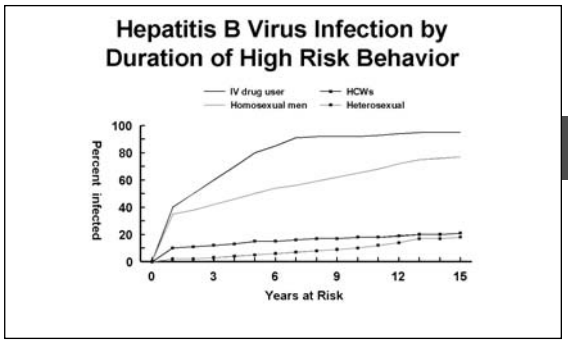
HEPATITIS B PREVENTION STRATEGIES

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, and the incidence of reported hepatitis B cases is now only slightly less than as it was before the vaccine was licensed.

The apparent lack of impact from the vaccine can be attributed to







several factors. From 1981 until 1991, vaccination was targeted to people in groups at high-risk of HBV infection. A large proportion of persons with HBV infection (25% to 30%) deny 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, there has been limited success in providing vaccine to persons in high-risk groups due to rapid acquisition of infection after beginning high-risk behaviors, low initial vaccine acceptance, and low completion rates.

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

A comprehensive strategy to eliminate hepatitis B virus transmission was recommended in 1991, and includes (a) prenatal testing of pregnant women for HBsAg to identify newborns who require immunoprophylaxis for the prevention of perinatal infection and to identify household contacts who should be vaccinated, (b) routine vaccination of infants, (c) vaccination of adolescents, and (d) vaccination of adults at high-risk of infection.

HEPATITIS B VACCINE

CHARACTERISTICS

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

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

Recombinant hepatitis B vaccine was licensed in the United States in July 1986, and was the first vaccine licensed in the United States produced by recombinant DNA technology. A second, similar vaccine was licensed in August 1989.

Hepatitis B Vaccine

• Composition	Recombinant HBsAg
• Efficacy	95% (Range, 80%-100%)
• Duration of Immunity	>15 years
• Schedule	3 Doses

- Booster doses not routinely recommended

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 and Company Vaccine Division (Recombivax HB) and GlaxoSmithKline Pharmaceuticals (Engerix-B). Both vaccines are available in both pediatric and adult formulations. Although the antigen content of the vaccines differ (see table below and in Appendix A), **vaccines made by different manufacturers are interchangeable**, except for the 2-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.

Hepatitis B Vaccine Formulations

- **Recombivax HB (Merck)**
  - **5.0 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)**

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 <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 (see table below and in Appendix A).

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 3-dose series, and by 60 years, only 75% of vaccinees develop protective antibody titiers. 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 Dose of Hepatitis B Vaccine

Group	Vaccine	
	Recombivax HB* Dose (mL)	Engerix-B* Dose (mL)
Infants† and children <11 years of age	5µg (0.5)	10µg (0.5)
Adolescents 11-19 years	5µg (0.5)	10µg (0.5)
Adults ≥20 years	10µg (1.0)	20µg (1.0)
Dialysis patients and other compromised persons	40µg§ (1.0)	40µg¶ (2.0)

* Usual schedule: Three doses at 0, 1, 6 months.
† Infants whose mothers are HBsAg positive should also receive hepatitis B immune globulin (HBIG) at birth.
§ Special formulation for dialysis patients.
¶ Two 1.0 ml doses given at one site in a four-dose schedule at 0, 1, 2, and 6 months.

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" length and to older children and adults of at least 1" length.

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 >15 years following immunization, and both adults and children with declining antibody levels are still protected against significant HBV infection (i.e., clinical disease, HBsAg antigenemia, or significant elevation of liver enzymes). Exposure to HBV results in an anamnestic anti-HBs response that prevents clinically significant HBV infection. Chronic HBV infection has only rarely been documented among vaccine responders.

Hepatitis B Vaccine

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 Vaccine
Routine Infant Schedule

Dose	Usual Age	Minimum Interval
Primary 1	0-2 months	---
Primary 2	1- 4 months	1 month
Primary 3	6-18 months	2 months

Hepatitis B vaccination is recommended for all infants soon after birth and before hospital discharge. Infants and children <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 with the second and third doses given 1 to 4 and 2 to 17 months, respectively, after the first. The first dose may be administered by age 2 months if the infant's mother is HBsAg-negative.

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** 2 months after the second dose, and should follow the first dose by at least 4 months. For infants, the **third dose should not be given earlier than 6 months 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 2 months after second dose, and
- At least 4 months after first dose, and
- For infants, at least 6 months of age

Premature infants born to HBsAg-positive women and women with unknown HBsAg status should receive immunoprophylaxis with hepatitis B vaccine and hepatitis B immune globulin (HBIG) beginning at or shortly after birth (see details below). For premature infants of HBsAg-negative mothers, the optimal timing of hepatitis B vaccination has not been determined. Some studies suggest that decreased seroconversion rates might occur in some premature infants with low birthweights (*i.e.*, <2000 grams) following administration of hepatitis B vaccine at birth. However, by chronological age 1 month, all premature infants, regardless of initial birth weight or gestational age are as likely to respond as adequately as older and larger children. Low birthweight infants of HBsAg-negative mothers can receive the first dose of the hepatitis B vaccine series at chronological age 1 month. Premature infants discharged from the hospital before chronological 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.

Very Low Birthweight Infants

- Infants <2000 grams respond poorly to vaccine
- Delay first dose until chronological age 1 month if mother HBsAg negative
- Birth dose and HBIG if mother HBsAg positive

COMVAX

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

COMVAX

- Hepatitis B-Hib combination
- Use when either antigen is indicated
- Cannot use <6 weeks of age
- May be used in infants whose mothers are HBsAg positive or status 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 Hib chapter for more details). COMVAX **must not be used for doses at birth or one month of age** for a child on a 0-1-6 month hepatitis B vaccine schedule. Although not labled by FDA, ACIP recommends that COMVAX may be used in infants whose mothers are HBsAg positive or whose HBsAg status is unknown.

PEDIARIX

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

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

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 one, two, or three of the series, and the child is less 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 in infants who received a birth dose of hepatitis B vaccine (total of 4 doses)
- May be used in infants whose mothers are HBsAg positive or status unknown

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 not known.

ADOLESCENTS

Routine hepatitis B vaccination is recommended for all children and adolescents through age 18 years. **All children not previously vaccinated with hepatitis B vaccine should be vaccinated at 11-12 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 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).

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 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 1.0 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 4 months.** Doses given at less than these minimum intervals should not be counted as part of the vaccination series.

Hepatitis B Vaccine Adolescent and Adult Schedule

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

*third dose must be separated from first dose by at least 4 months

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

Alternative Adolescent Vaccination Schedule

- Two 10 mcg doses of Recombivax HB separated by 4-6 months
- May only be used for adolescents 11-15 years of age
- Only applies to Merck hepatitis B vaccine

ADULTS

Routine pre-exposure 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 1.0 mL (10 mcg) of pediatric or adult formulation Recombivax HB (Merck) or 1.0 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 4 months.** 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 who are at increased risk of HBV infection from sexual transmission include **men who have sex with other men, heterosexuals with multiple sexual partners, persons diagnosed with a recently acquired sexually transmitted disease, and prostitutes.**

Adult Hepatitis B Vaccine Candidates

- Men who have sex with men
- Heterosexual with multiple partners
- Persons diagnosed with an STD
- Prostitutes
- Injection drug users
- Male prison inmates
- Persons receiving dialysis
- Healthcare workers

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

Long-term male prison inmates are at increased risk of HBV

infection because of injection drug use, homosexual activity, or other factors. The prison setting provides an access point for vaccination of inmates with histories of high-risk behavior.

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

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

OTHER GROUPS WHO MAY BE CANDIDATES FOR HEPATITIS B VACCINE

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

15

Adult Hepatitis B Vaccine Candidates

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

*from countries of high or intermediate HBV endemnicity

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

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

Household members and sexual partners of HBV carriers should be tested and, if susceptible, should be vaccinated.
Adults and children who plan to travel to areas outside the United States that have high rates of HBV infection should be vaccinated if they plan to stay in these areas for more than 6 months and have close contact with the local population. Persons traveling

for shorter durations who may have sexual contact with local persons in areas where HBV infection is common should also be vaccinated. Persons traveling abroad who will perform medical procedures in areas where HBV infection is common are at very high risk.

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

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

SEROLOGIC TESTING OF VACCINE RECIPIENTS

PREVACCINATION SEROLOGIC TESTING

The decision to screen potential vaccine recipients for prior infection depends on the cost of vaccination, the cost of testing for susceptibility, and the expected prevalence of immune persons in the group. Screening is usually cost-effective, and should be considered, in groups with a high risk of HBV infection (HBV markers prevalence >20%) such as male homosexuals, injection drug users, Alaskan natives, Pacific Islanders, children of immigrants from endemic countries, and family members of HBsAg carriers. 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
- May be considered when vaccinating adolescents in groups with high rates of HBV infection
  - Alaskan Natives
  - Pacific Islanders
  - Children of immigrants from endemic countries
  - Family members of HBV carriers

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 knowing their immune status, such as dialysis patients and staff, and persons in whom a suboptimal response may be anticipated, such as those who have received vaccine in the buttock. When necessary, postvaccination testing should be performed 1-2 months after completion of the vaccine series.

Postvaccination Serologic Testing

- Not routinely recommended following vaccination of infants, children, adolescents, or most adults
- Recommended for:
  - Infants born to HBsAg+ women
  - Dialysis patients
  - Immunodeficient persons
  - Certain healthcare workers

All infants born to HBsAg-positive women should be tested 3-9 months after their final (third or fourth) dose of hepatitis B vaccine (*i.e.*, at 9-15 months of age). If HBsAg is not present and anti-HBs antibody is present, children can be considered to be protected.

In 1997, ACIP and the Hospital Infection Control Practices Advisory Committee published comprehensive recommendations

Postvaccination Serologic Testing

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

for the immunization of health care workers. One of the recommendations was that **healthcare workers who have contact with patients or blood and are at ongoing risk for injuries with sharp instruments or needlesticks should be routinely tested for antibody after vaccination.** However, a catch-up program of serologic testing for healthcare providers vaccinated prior to December 1997 is not recommended. These individuals 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

Management of Nonresponse to Hepatitis B Vaccine

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

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), male gender, 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% 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 at the completion of the second vaccine series.

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

Fewer than 5% of persons receiving 6 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 6 doses may have a low level of antibody that is not detected by routine serologic testing ("hyporesponder"). 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 6 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 3-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 below).

It is difficult to interpret the meaning of a negative anti-HBs serology in a person who received hepatitis B in the past and was not tested after vaccination. Without postvaccination testing, it is not possi-

ble to determine if persons testing negative years after vaccination represent true vaccine failure (i.e., no initial response), or have waned anti-HBs antibody 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 individuals. Serology for anti-HBs antibody should be repeated 1-2 months after the 6th 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, then a second series should be completed (*i.e.*, 2 more doses). If the person is still seronegative after 6 total doses, he or she should be managed as a nonresponder (see Postexposure Management, below).

POSTEXPOSURE MANAGEMENT

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

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 9-15 months of age

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 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 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 to 15 months of age (3 to 9 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 kilograms 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 9-15 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 (<2000 grams birth weight) 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 less reliable immune resonse in preterm infants weighing <2000 grams. As described above, the vaccine dose administered at birth should not be counted as part of the series, and the infant should receive 3 additional doses beginning at age 1 month. The vaccine series should be completed by 6 months of age.

There are few data 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 not known (see http://www.cdc.gov/nip/vfc/acip_recs/1003hepb.pdf. **COMVAX and Pediarix should never be used in infants <6 weeks of age**. Either vaccine may be administered at the same time as other childhood vaccines given at ≥6 weeks of age.

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

Recommended Postexposure Prophylaxis for Exposure to Hepatitis B Virus

Vaccination and antibody status of exposed person*		Treatment		
		Source HBsAg** Positive	Source HBsAg** Negative	Source unknown or not available for testing
Unvaccinated		HBIG† X 1 and initiate HB vaccine series	Initiate HB vaccine series	Initiate HB vaccine series
Previously Vaccinated	Known Responder §	No treatment	No treatment	No treatment
	Known non-responder ‡	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

SUSCEPTIBLE SEXUAL PARTNERS OF PERSONS WITH ACUTE HBV INFECTION, OR HEPATITIS B CARRIERS

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

HOUSEHOLD CONTACTS OF PERSONS WITH ACUTE HBV INFECTION

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

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 hepa-

titis B surface antigen protein (equivalent to an adult dose of Engerix-B). The vaccine is administered in a 3-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 B (adult dose) and hepatitis A vaccine (pediatric dose)
- Schedule: 0, 1, 6-12 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.

ADVERSE REACTIONS FOLLOWING VACCINATION

The most common adverse reaction following hepatitis B vaccine is **pain at the site of injection,** reported in 13% to 29% of adults and 3% to 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. Low-grade fever (>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 >37.7 C	1%	0.4%-6%
Severe systemic reactions	rare	rare

Hepatitis B vaccine has been alleged to cause or exacerbate multiple sclerosis. However, recent large population-based studies have shown there is no association between receipt of hepatitis B vaccine and either the development of multiple sclerosis or exacerbation of the course of multiple sclerosis is persons already diagnosed with the disease.

CONTRAINDICATIONS AND PRECAUTIONS TO VACCINATION

A serious 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 conditions improve. 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 2°- 8°C (35°-46°F), but not frozen. Exposure to freezing temperature destroys the potency of the vaccine.

HEPATITIS B IMMUNE GLOBULIN

Hepatitis B immune globulin (HBIG) is prepared by cold ethanol fraction of plasma from selected donors with high anti-HBs titers; contains an anti-HBs titer of at least 1:100,000, by RIA. It is used for passive immunization for (1) accidental (percutaneous, mucous membrane) exposure, (2) sexual exposure to HBsAg-positive person, (3) perinatal exposure of infant, or (4) household exposure of an infant less 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.

MATERNAL SCREENING

In 1988, the Advisory Committee on Immunization Practices (ACIP), in consultation with the American College of Obstetrics and Gynecology and the American Academy of Pediatrics, recommended that all pregnant women should be routinely tested for HBsAg during an early prenatal visit, in each pregnancy. If a woman has not been screened prenatally, or the results are unavailable at the time of delivery, HBsAg testing should be done at admission for delivery. This identifies infants born to HBsAg positive mothers for prompt prophylaxis at birth, as well as at 1 and 6 month follow-ups. Also, household members and sexual partners of HBV carriers should be evaluated for the need for hepatitis B vaccine.

SELECTED REFERENCES

American Academy of Pediatrics. Hepatitis B. In: Pickering L ed. *Red Book: 2003 Report of the Committee on Infectious Diseases*. 26th ed. Elk Grove Village, IL: American Academy of Pediatrics, 2003:318-36.

Ascherio A, Zhang SM, Hernan MA, et al. Hepatitis B vaccination and the risk of multiple sclerosis. *N Engl J Med* 2001;344:327-32.

CDC. Hepatitis B virus: a comprehensive strategy for eliminating transmission in the United States through universal childhood vaccination. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 1991;40(RR-13):1-25. (currently being revised)

CDC. Immunization of health-care workers. Recommendations of the Advisory Committee on Immunization Practices (ACIP) and the Hospital Infection Control Practices Advisory Committee (HICPAC). *MMWR* 1997;46(RR-18):1-42.

CDC. Updated U.S. Public Health Service guidelines for the management of occupational exposures to HBV, HCV, and HIV and recommendations for postexposure prophylaxis. *MMWR* 2001;50(RR-11):1-42.

Confavreux C, Suissa S, Saddier P, et al. Vaccinations and the risk of relapse in multiple sclerosis. *N Engl J Med* 2001;344:319-26.

Margolis HS, Alter MJ, Hadler SC. Viral hepatitis. In: Evans AS, Kaslow RA, eds. *Viral Infections of Humans. Epidemiology and Control*. 4th edition. New York, NY: Plenum Medical Book Company, 1997.

Lee WM. Hepatitis B virus infection. *N Engl J Med* 1997;337:1733-45.

Lewis E, Shinefield HR, Woodruff BA, et al. Safety of neonatal hepatitis B vaccine administration. *Pediatr Infect Dis J* 2001;20:1049-54.

Mast E, Mahoney F, Kane M, Margolis H. In: Plotkin SA, Orenstein WA, eds. *Vaccines*. 4th edition. Philadelphia, PA: Saunders; 2003:299-337.

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 world-wide epidemic, that clearly fits the description of influenza was in 1580. At least four pandemics of influenza occurred in the 19th century, and 3 occured in the 20th century. The pandemic of "Spanish flu" 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. Evidence of the protective efficacy of inactivated vaccines was produced in the 1950s. The first live attenuated influenza vaccine was licensed in 2003.

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, such as pigs and birds. **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.

ANTIGENIC CHANGES

Hemagglutinin and neuraminidase periodically change, apparently due to sequential evolution within immune or partially immune populations. Antigenic mutants emerge and are selected as the predominant virus to the extent that they differ from the antecedent virus, which is suppressed by specific antibody arising in the population. 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.

Influenza

- Highly infectious viral illness
- Epidemics reported since at least 1510
- At least 4 pandemics in 19th century
- Estimated 21 million deaths worldwide in pandemic of 1918-1919
- Virus first isolated in 1933

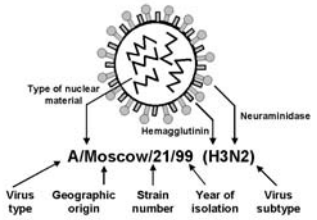
Influenza Virus

- Single-stranded RNA virus
- Family Orthomyxoviridae
- 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 epidemics
  - humans only
  - primarily affects children
- Type C- rarely reported in humans
  - no epidemics

Influenza Virus



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 1997, A/Wuhan/359/95 (H3N2) virus was dominant
  - A/Sydney/5/97 (H3N2) appeared in late 1997 and became the dominant virus in 1998

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

Antigenic shift is a major change in one or both surface antigens (H and/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.

Antigenic drift is a minor change in surface antigens that result from point mutations in a gene segment. Antigenic drift may result in epidemics, since incomplete protection remains from past exposures to similar viruses. 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.

In the past 100 years, there have been 4 antigenic shifts that 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 (except for the 1918-1919 strain), but because large numbers of people 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 **epidemics**, 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, with an increase in visits to healthcare providers. 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 localize to families, schools, and isolated communities.

PATHOGENESIS

Following respiratory transmission, the virus attaches to and pene-

trates 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 to 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 around 50% of infected persons will develop the classic clinical symptoms of influenza.

"Classic" influenza disease is characterized by the abrupt onset of fever, myalgia, sore throat, and nonproductive cough. 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).

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

Systemic symptoms and temperature 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 may have lingering depression and asthenia (lack of strength or energy) for several weeks.

COMPLICATIONS

The most frequent complication of influenza is pneumonia, most commonly **secondary bacterial pneumonia** (*e.g.*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Staphylococcus aureus*). **Primary influenza viral pneumonia** is an uncommon complication with a high fatality rate. **Reye syndrome** is a complication that occurs almost exclusively in children taking aspirin, primarily in association with influenza B (or varicella zoster), and presents with severe vomiting and confusion which may progress to coma, due to swelling of the brain.

Influenza Complications

- Pneumonia
  - primary influenza
  - secondary bacterial
- Reye syndrome
- Myocarditis
- Death 0.5-1 per 1000 cases

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 1000 cases. The majority of deaths occur in persons ≥65 years of age.

IMPACT OF INFLUENZA

An increase in mortality typically accompanies an influenza epidemic. Increased mortality results not only from influenza and pneumonia, but also from cardiopulmonary and other chronic diseases that can be exacerbated by influenza.

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

Impact of Influenza

- Highest rates of complications and hospitalization among young children and person ≥65 years
- Average of 114,000 influenza-related excess hospitalizations per year since 1969
- 57% of all hospitalizations among persons <65 years of age
- Greater number of hospitalizations during type A (H3N2) epidemics

Hospitalization Rates for Influenza By Age and Risk Group*

Age Group	Rate** (high-risk)	Rate** (not high-risk)
0-11 mos	1900	496-1038
1-2 yrs	800	186
3-4 yrs	320	86
5-14 yrs	92	41
15-44 yrs	56-110	23-25
45-64 yrs	392-635	13-23
≥65 yrs	399-518	125-228

* Data from several studies 1972 - 1995
** Hospitalizations per 100,000 population

Influenza Diagnosis

- Clinical and epidemiological characteristics
- Isolation of influenza virus from clinical specimen (e.g., nasopharynx, throat, sputum)
- Significant risk in influenza IgG by serologic assay
- Direct antigen testing for type A virus

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.

The risk for complications and hospitalizations from influenza are higher among persons 65 and older, young children, and persons of any age with certain underlying medical conditions. An average of 114,000 hospitalizations per year are related to influenza, more than 50% of which are among persons aged 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 percent, with fatality rates as high as 30 percent. The cost of a severe epidemic has been estimated to be 12 billion dollars.

Among children aged 0-4 years, hospitalization rates have ranged from 100 per 100,000 healthy children to as high as 500 per 100,000 for children with underlying medical conditions. Hospitalization rates for children 12 months of age and younger are comparable to rates among persons 65 and older.

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.

LABORATORY DIAGNOSIS

The diagnosis of influenza is usually suspected on the basis of characteristic clinical findings, particularly if influenza has been reported in the community.

Virus can be isolated from throat and nasopharyngeal swabs obtained within 3 days of onset of illness. Culture is performed by inoculation of amniotic or allantoic sac of chick embryos or certain cell cultures that support viral replication. A minimum of 48 hours are 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 specimen should be taken less than 5 days from onset and a convalescent specimen taken 10-21 days, or, (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 4-fold 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.

EPIDEMIOLOGY

OCCURRENCE

Influenza occurs throughout the world.

RESERVOIR

Humans are the only known reservoir of influenza types B and C. Influenza A may infect both humans and animals. There is no chronic carrier state.

TRANSMISSION

Influenza is transmitted via aerosolized or droplet transmission from the respiratory tract of infected persons. A less important mode of transmission of droplets is by direct contact.

TEMPORAL PATTERN

Influenza activity peaks from December to March in temperate climates, but may occur earlier or later. During 1976-2002, peak influenza activity in the United States occurred most frequently in January (23% of seasons) and February (42% of seasons). However, peak influenza activity occurred in March, April, or May in 20% of seasons. Influenza occurs throughout the year in tropical areas.

COMMUNICABILITY

Maximum communicability occurs 1-2 days before onset to 4-5 days thereafter.

SECULAR TRENDS IN THE UNITED STATES

There is a documented association between influenza and increased morbidity in "high-risk" adults. Hospitalization for adults with high-risk medical conditions increases 2-fold to 5-fold during major epidemics.

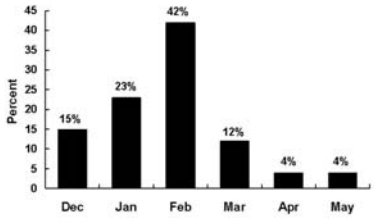
The impact of influenza in the United States is quantified by measuring pneumonia and influenza (P and I) deaths. Death certificate data are collected from 122 U.S. cities with populations of ≥100,000 (approximately 70,000,000). P and I deaths include all deaths for which pneumonia is listed as a primary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

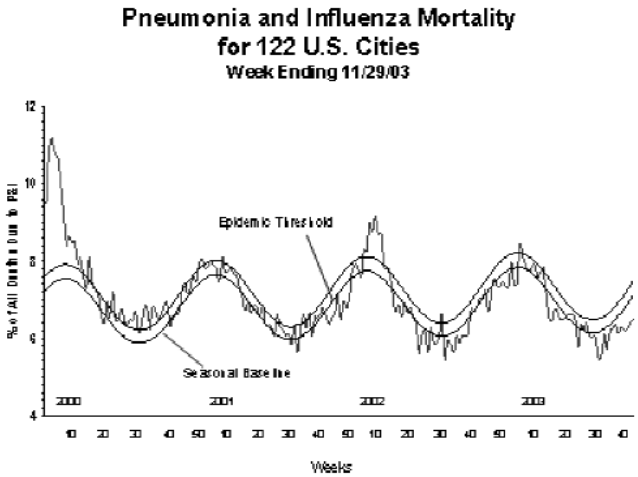
Influenza Epidemiology

- Reservoir — Human, animals (type A only)
- Transmission — Respiratory; Probably airborne
- Temporal pattern — Peak December - March in temperate area; May occur earlier or later
- Communicability — Maximum 1-2 days before to 4-5 days after onset

Month of Peak Influenza Activity – United States, 1976-2002



dard deviations above the values projected on the basis of a periodic regression model applied to 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. Split vaccines are associated with fewer adverse reactions among children, than previously-produced whole virus vaccines. 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) formulations. TIV is available with thimerosal as a preservative, and in reduced and preservative free formulations.

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 (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 daycare 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 it's 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 rarely exceeds 1 year. 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 young adult vaccinees from illness when the vaccine strain is similar to the circulating strain. However, the vaccine is only 30%-40% effective in preventing illness among frail elderly persons.

Although the vaccine is not highly effective in prevention of clinical illness among the elderly, it is effective in prevention of 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 vaccinated residents.

LAIV

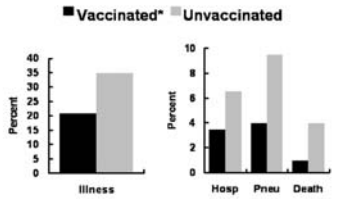
LAIV has been tested in groups of both healthy children and healthy adults. A randomized, double-blind, placebo-controlled trial in healthy children 60-84 months of age assessed the efficacy of the trivalent LAIV against culture confirmed influenza during two influenza seasons. In year one, when vaccine and circulating virus strains were well matched, efficacy was 87% against culture confirmed influenza. In year two, 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.

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.

Inactivated Influenza Vaccine Efficacy

- 70%-90% effective among healthy persons <65 years of age
- 30%-40% effective among frail elderly persons
- 50%-60% effective in preventing hospitalization
- 80% effective in preventing death

Influenza and Complications Among Nursing Home Residents



*Inactivated influenza vaccine. Genesee County, MI, 1982-1983

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

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. Organized campaigns for high-risk persons who are routinely accessible are optimally undertaken in October and November. The ACIP recommends that high-risk persons, healthcare workers, and children <9 years old being vaccinated for the first time, should begin vaccinations in October. All other groups should begin vaccinations in November. Vaccine may be given up to and even after influenza activity is documented in a region. Although most influenza vaccination activities should be completed by December (particularly for high-risk persons), providers should continue to provide vaccine throughout influenza season.

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

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.

TIV is recommended for **all persons 50 years of age or older**, 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 Reyes syndrome following influenza infection).

Inactivated Influenza Vaccine Recommendations

- All persons 50 years of age or older
- 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

Persons >6 months of age with a chronic illness should receive TIV anually. 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
- hemoglobinopathies, such as sickle cell disease
- immunosuppression.

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
  - hemoglobinopathies
  - immunosuppression, including HIV infection

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 4 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 ≥14 weeks gestation during influenza season

ACIP recommends vaccination of women who will be in at least the 14th week or later of gestation during influenza season. Influenza season in the United States generally occurs in December through March. Therefore, women who become pregnant between March and December are TIV candidates. Pregnant women who have high-risk medical conditions should receive TIV before influenza season regardless of the stage of pregnancy. **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 higher 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

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

Influenza Vaccine Recommendations

- Healthcare providers, including home care (TIV only)
- Employees of long-term care facilities (TIV only)
- Household members of high-risk persons including children 0-23 months (TIV or LAIV*)

*household and other close contacts of immunosuppressed persons should not receive LAIV

Groups that have contact with high-risk persons should receive TIV. These groups include **healthcare workers, employees of long-term care facilities, and household members of high-risk persons.** These individuals may be younger and healthier, and more likely to be protected from illness than 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 should not be administered to persons with close contact with immunosuppressed persons (*e.g.*, healthcare workers or household contacts).**

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. **Foreign travelers** 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 elegible for LAIV (see below).

Influenza Vaccine Recommendations*

- Providers of essential community services
- Foreign travelers
- Students
- Anyone who wishes to reduce the likelihood of becoming ill from influenza

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

Beginning in 2002, the ACIP encouraged healthy children aged 6-23 months be vaccinated because they are at increased risk of influenza-related hospitalization. Household contacts and other caregivers of children <24 months of age are also encouraged to receive annual influenza vaccination. Beginning in influenza season 2004-2005, ACIP will recommend (rather than encourage) routine annual influenza vaccination of all children 6-23 months of age. Only TIV should be used for this age group.

Influenza Vaccination of Children

- Children <24 months at increased risk of hospitalization
- Inactivated influenza vaccination of healthy children 6-23 months is encouraged*
- Vaccination of household contacts and out-of-home caretakers is encouraged

*Beginning in influenza season 2004-2005, routine annual influenza vaccination (TIV) of children 6-23 months of age will be recommended rather than "encouraged"

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 for persons 9-49 years of age. Children 5-8 years of age receiving influenza vaccine for the first time should receive two doses administered 6-10 weeks apart.

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

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

*LAIV or inactivated vaccine

Live Attenuated Influenza 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

Live attenuated influenza vaccine is approved by the Food and Drug Administration only for use among healthy persons 5-49 years of age. 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 for 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 individuals. There are no data assessing the risk of transmission of LAIV from vaccine recipients to immunosuppressed contacts. **In the absence of such data, use of inactivated influenza vaccine is preferred for vaccinating household members, healthcare workers, and others who have close contact with immunosuppressed individuals.** This preference is because of the theoretical risk that a live attenuated vaccine virus could be transmitted to the immunosuppressed individual and cause disease. ACIP states no preference between inactivated vaccine and LAIV for vaccination of healthy persons aged 5 to 49 years in close contact with all other high-risk groups.

Vaccination of Healthcare Workers and Close Contacts of Immunosuppressed Persons

- No data regarding transmission from adults vaccinated with LAIV to immunosuppressed persons
- ACIP prefers the use of inactivated influenza vaccine for persons with household or other close contact with immunosuppressed persons, including healthcare workers

The manufacturer's package insert recommends that LAIV not be administered concurrently with other vaccines, because it is not known whether concurrent administration of LAIV with other vaccines affects the safety or efficacy of either LAIV or the simultaneously administered vaccine. In the absence of specific data indicating interference, ACIP recommends that providers follow the simultaneous administration guidelines published in the General Recommendations on Immunization. Inactivated vaccines do not interfere with the immune response to live vaccines. Inactivated vaccines such as tetanus and diphtheria toxoids can be administered either simultaneously or at any time before or after LAIV. Other live vaccines can be administered at the same visit 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 at the same visit 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 myalgias are reported in <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 systemic symptoms are no more common than in persons given a placebo injection.

Inactivated Influenza Vaccine Adverse Reactions

• Local reactions	15%-20%
• Fever, malaise	uncommon
• Allergic reactions	rare
• Neurological reactions	very rare

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 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 among persons with severe egg allergy. Persons who have developed hives, had swelling of the lips or tongue, or 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 persons without such a history irrespective of vaccination. As a result, the likelihood of coincidentally developing GBS after influenza vaccination is expected to be greater among persons with a history of GBS than among persons with no history of GBS. Whether influenza vaccination might be causally associated with this risk for recurrence is not known. It seems prudent for persons known to have developed GBS within 6 weeks of a previous influenza vaccination to avoid subsequent influenza vaccination. For most persons with a history of GBS who are at high risk for severe complications from influenza the established benefits of influenza vaccination justify yearly vaccination.

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

LAIV

The safety of the approved LAIV has been assessed in 20 prelicensure clinical trials. More than 6,000 study participants were in the approved age range of 5-49 years. Among healthy children, there were no significant differences between vaccine and placebo recipients in the proportion with upper respiratory symptoms such as runny nose and nasal congestion, fever, or other systemic symptoms. These symptoms were reported in 10%-40% of both vaccine and placebo recipients. Data from an unpublished study suggested **a significantly increased risk of asthma or reactive airways disease among children 12-59 months of age** who received LAIV. Because of this, LAIV is not approved for use in children less 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 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, and generally 3%-10% higher than in 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.

There have been no instances of Guillain-Barré syndrome reported among LAIV recipients. However the number of persons vaccinated to date is too small to identify such a rare vaccine adverse reaction.

There are few data 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 is available, persons at high risk of complications of influenza should not receive LAIV. These persons should continue to receive inactivated influenza vaccine.

CONTRAINDICATIONS AND PRECAUTIONS TO VACCINATION

TIV

Persons with a **severe allergic reaction** to a prior dose of inactivated influenza vaccine, or to a vaccine component (*e.g.*, eggs) should not receive TIV. Persons with a **moderate or severe acute illness** normally should not be vaccinated until their symptoms have decreased. Neither pregnancy nor breastfeeding is a contraindication to inactivated influenza vaccination.

Inactivated Influenza Vaccine Contraindications and Precautions

- Severe allergic reaction to a vaccine component (e.g., egg) or following a prior dose of vaccine
- Moderate or severe acute illness

Live Attenuated Influenza Vaccine Contraindications and Precautions

- Children <5 years of age*
- Persons ≥50 years of age*
- Persons with underlying medical conditions*
- Children and adolescents receiving chronic 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

LAIV

Persons who should **not** receive LAIV include children less than 5 years of age; persons 50 years of age and older; and 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 hemoglobinopathies, such as sickle cell disease; and children or adolescents receiving chronic 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, persons who are immunosuppressed because of disease, including HIV, or who are receiving immunosuppressive therapy, should not receive LAIV. 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 nasal congestion is present that 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 antivirals 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 (2°-8°C [35°-46°F]). **Inactivated influenza vaccine must not be frozen**. Opened multidose vials may be used until the expiration date printed on the package if not visibly contaminated.

LAIV

LAIV must be stored at or below -15°C (+5°F) at all times. The vaccine is shipped from the manufacturer with dry ice, and it should be frozen on arrival at the provider's office. The manufacturer recommends that LAIV not be stored in a frost-free freezer because the temperature in these units may rise above -15° C during the defrost

cycle. LAIV must be stored only in a manual defrost freezer that can reliably maintain -15°C (+5°F). **If a manual defrost freezer is not available, LAIV must be stored in a special manufacturer-supplied freezer box.** The freezer box is made of special insulating material that will protect LAIV from the temperature of defrost cycles in a self-defrosting freezer. Contact the manufacturer for more information about the availability and use of a freezer box.

In general, LAIV should be kept frozen until immediately before it is used, at which time it should be thawed by holding the sprayer in the palm of a hand. The sprayer should not be rolled between the palms because this could dislodge the dose divider clip or plunger. LAIV may also be thawed in a refrigerator. However, it can be stored at refrigerator temperature (2°-8°C) for no more than 24 hours prior to use. Any LAIV that is kept at refrigerator temperature more than 24 hours must be discarded.

LAIV Storage and Handling

- Must be stored at ≤ -15° C (+5° F) at all times
- Do NOT store in a frost-free freezer
- Store ONLY in a MANUAL defrost freezer
- If no manual defrost freezer, must store LAIV in special freezer box supplied by the manufacturer

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 2001, 64% of persons 65 years of age and older reported influenza vaccine in the previous year. Vaccination levels were lower in black and Hispanic persons than among non-Hispanic white persons.

STRATEGIES FOR IMPROVING INFLUENZA VACCINE COVERAGE

Up to 75% of persons at high risk for influenza or who die from pneumonia and influenza may have received care in a physician's office during the previous year. One study indicated that all persons who died from pneumonia or influenza and did not reside in a nursing home, had at least one medical visit during the previous year.

An average of less than 20% of persons in high-risk groups receive influenza vaccine each year. More effective strategies for delivering vaccine to high-risk persons, their healthcare providers, and household contacts are needed. 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

OUTPATIENT CLINICS AND PHYSICIANS' OFFICES

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.

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.

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

Persons providing home care should identify high-risk patients and administer TIV in the home, if necessary.

FACILITIES PROVIDING SERVICES TO PERSONS AGED ≥ 50 YEARS

Inactivated influenza vaccine should be offered to all unvaccinated residents or attendees on site at facilities providing services to persons ≥50 years of age *(e.g.,* retirement communities, recreation centers). Education and publicity programs should also be conducted in conjunction with other interventions.

HEALTHCARE FOR TRAVELERS

Indications for influenza vaccine should be reviewed prior to travel and vaccine offered, if appropriate.

Administrators of all of the above facilities and organizations should arrange for influenza vaccine to be offered to all personnel before the influenza season. Additionally, household members of high-risk persons and others with whom they will be in contact should receive written information about why they should receive the vaccine and where to obtain it.

ANTIVIRAL AGENTS FOR INFLUENZA

In the United States, four antiviral agents are approved for preventing or treating influenza: amantadine, rimantadine, zanamivir, and oseltamivir. Amantadine and rimantadine are effective against type A influenza only, and are approved by the Food and Drug Administration for both influenza A prophylaxis and treatment in persons 1 year of age and older.

Zanamivir and oseltamivir are members of a new class of drugs called neuraminidase inhibitors, and are active against both influenza type A and type B. Zanamivir is provided as a dry powder that is administered by inhalation. It is approved for treatment of uncomplicated acute influenza A or B in persons 7 years of age and older who have been symptomatic for no more than 2 days. 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 2 days. Oseltamivir is approved for prophylaxis of influenza infection among persons ≥13 years. Zanamivir is not approved for prophylaxis.

Influenza Antiviral Agents

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

Antiviral agents for influenza are an adjunct to vaccine and are not a substitute for vaccine. Vaccination remains the principal means for preventing influenza-related morbidity and mortality. Additional information on the use of influenza antiviral drugs can be found in the current ACIP statement on influenza vaccine.

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 not immunized or immunized too recently to have protective antibody levels. Antivirals 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 (1) monitor the prevalence of circulating strains and to detect new strains necessary for vaccine formulation; (2) estimate influenza-related impact on morbidity, mortality, and economic loss; (3) rapidly detect outbreaks; and (4) assist disease control through rapid preventive action (*e.g.*, chemoprophylaxis of unvaccinated high-risk patients).

Influenza Surveillance

- Monitor prevalence of circulating strains and detect new strains
- Rapidly detect outbreaks
- Assist disease control through rapid preventive action
- Estimate influenza-related morbidity, mortality and economic loss

CDC receives weekly surveillance reports from the states showing the extent of influenza activity. Reports are classified into four categories: (1) no cases, (2) sporadic, (3) regional (cases occurring in counties collectively contributing less than 50% of a state's population), (4) widespread (cases occurring in counties collectively contributing 50% or more of a state's population).

SENTINEL FAMILY PHYSICIAN NETWORK

Physicians nationwide provide weekly telephone information about the number of cases and hospitalizations that have occurred in their practices; a subgroup of physicians collect nasopharyngeal specimens from selected cases for submission to the Centers for Disease Control and Prevention (CDC) for culture confirmation.

LABORATORY SURVEILLANCE

More than 100 World Health Organization (WHO) Collaborating Laboratories in the U.S. regularly submit reports on the number of specimens tested and the number and type of influenza viruses isolated for each week from early October through mid-May to the WHO Collaborating Center for Influenza at CDC.

SELECTED REFERENCES

American Academy of Pediatrics. Influenza. In Pickering L, ed. *Red Book: 2003 Report of the Committee on Infectious Diseases.* 26th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2003:382-91.

Belshe RB, Mendelman PM, Treanor J, et al. Efficacy of live attenuated, cold-adapted trivalent, intranasal influenza virus vaccine in children. *N Engl J Med* 1998;338:1405-12.

CDC. Prevention and control of influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2003;52(No. RR-8):1-34. Note: ACIP recommendations for influenza vaccine are revised annually.

CDC. Immunization of health-care workers. Recommendations of the Advisory Committee on Immunization Practices (ACIP) and the Hospital Infection Control Practices Advisory Committee (HICPAC). *MMWR* 1997;46(RR-18):1-42.

CDC. Using live attenuated influenza vaccine for prevention and control of influenza. *MMWR* 2003;52(No. RR-13):1-8.

Fedson DS, Houck P, Bratzler D. Hospital-based influenza and pneumococcal vaccination: Sutton's law applied to prevention. *Infect Control Hosp Epidemiol* 2000;21:692-699.

Glezen WP, Couch RB. Influenza viruses. In: Evans AS, Kaslow RA, eds. *Viral Infections of Humans. Epidemiology and Control.* 4th edition. New York, NY: Plenum Medical Book Company; 1997:473-505.

McBean AM, Babish JD, Warren JL. The impact and cost of influenza in the elderly. *Arch Intern Med* 1993;153:2105-11.

Murphy KR, Strunk RC. Safe administration of influenza vaccine in asthmatic children hypersensitive to egg protein. *J Pediatr* 1985;106:931-933.

Neuzil KM, Zhu Y, Griffin MR, et al. Burden of interpandemic influenza in children younger than 5 years: a 25 year prospective study. *J Infect Dis* 2002;185:147-52.

Nichol KL, Lind A, Margolis KL, et al. The effectiveness of vaccination against influenza in healthy, working adults. *N Eng J Med* 1995;333:889-93.

Saxen H, Virtanen M. Randomized, placebo-controlled double blind study on the efficacy of influenza immunization on absenteeism of healthcare workers. *Pediatr Infect Dis J* 1999;18:779-83.

Thompson WW, Shay DK, Weintraub E, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. *J Am Med Assoc* 2003;289:179-86

Disease caused by *Streptococcus pneumoniae* results in wide-spread illness and death throughout the United States each year. The bacterium, also called pneumococcus, was first identified by Pasteur in 1881 from the saliva of a patient with rabies. The association between the pneumococcus bacterium and lobar pneumonia was first described by Friedlander and Talamon in 1883, but pneumococcal pneumonia was confused with other types of pneumonia until the discovery of the Gram stain in 1884. From 1915 to 1945, the chemical structure and antigenicity of the pneumococcal capsular polysaccharide, its association with virulence, and the role of bacterial polysaccharides in human disease were explained. More than 80 serotypes of pneumococci had been described by 1940.

Pneumococcal Disease

- *S. pneumoniae* first isolated by Pasteur in 1881
- Confused with other causes of pneumonia until discovery of Gram stain in 1884
- More than 80 serotypes described by 1940
- First U.S. vaccine in 1977

Efforts to develop effective pneumococcal vaccines began as early as 1911. However, with the advent of penicillin in the 1940s, interest in the vaccine declined, until it was observed that many patients still died despite antibiotic treatment. By the late 1960s, efforts were again being made to develop a polyvalent pneumococcal vaccine. The first pneumococcal vaccine was licensed in the United States in 1977. The first conjugate pneumococcal vaccine was licensed in 2000.

STREPTOCOCCUS PNEUMONIAE

Streptococcus pneumoniae 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 to additional serotypes.

Streptococcus pneumoniae

- Gram-positive bacteria
- 90 known serotypes
- Polysaccharide capsule important virulence factor
- Type-specific antibody is protective

Most *S. pneumoniae* serotypes have been shown to cause serious disease, but only a few serotypes produce the majority of pneumococcal infections. The 10 most common serotypes are estimated to account for about 62% of invasive disease worldwide. The ranking and serotype prevalence differs by age group and geographic area. In the United States the seven most common serotypes isolated from the blood or cerebrospinal fluid (CSF) of children <6 years of age account for 80% of infections. These 7 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 normal

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% to 58% of students and residents may be carriers. On military installations, as many as 50% to 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.

Pneumococcal Pneumonia
Clinical Features

- Abrupt onset
- Fever
- Shaking chill
- Productive cough
- Pleuritic chest pain
- Dyspnea, tachypnea, hypoxia

CLINICAL FEATURES

The major clinical syndromes of pneumococcal disease include **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

- Estimated 175,000 hospitalized cases per year
- 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

Pneumococcal pneumonia is the most common clinical presentation of pneumococcal disease among adults. 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.

Up to an estimated 175,000 hospitalized cases of pneumococcal pneumonia occur annually in the United States. Pneumococci account for up to 36% of adult community-acquired pneumonia and 50% of hospital-acquired pneumonia. It is a common bacterial complication of influenza and measles. The case-fatality rate is 5%-7%, and may be much higher in 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 mortality rate for bacteremia is about 20%, but may be as high as 60% in elderly patients. Patients with asplenia who develop bacteremia may experience a fulminant clinical course.

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

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-quarter 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 mortality rate of pneumococcal meningitis is about 30%, but may be as high as 80% in elderly persons. Neurologic sequelae are common among survivors.

PNEUMOCOCCAL DISEASE IN CHILDREN

Bacteremia without a known site of infection is the most common invasive clinical presentation among children <2 years of age, 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. With the decline of invasive Hib disease, *S. pneumoniae* has become the leading cause of bacterial meningitis among children <5 years of age in the United States. Before routine use of pneumococcal conjugate vaccine, children <1 year had the highest rates of pneumococcal meningitis, approximately 10 cases per 100,000 population.

Pneumococci are a common cause of acute otitis media, and are detected in 28%-55% of middle ear aspirates. By age 12 months, 62% 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 <5 years of age was significant. An estimated 17,000 cases of invasive disease occured each year, of which 13,000 were bacteremia without a known site of infection and about 700 were of 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 occur each year among children <5 years of age.

Pneumococcal Disease in Children

- **Bacteremia without known site of infection most common clinical presentation**
- ***S. pneumoniae* leading cause of bacterial meningitis among children <5 years of age**
- **Common cause of acute otitis media**

Burden of Pneumococcal Disease in Children*

Syndrome	Cases
•Bacteremia	13,000
•Meningitis	700
•Death	200
•Otitis media	5,000,000

*Prior to routine use of pneumococcal conjugate vaccine

LABORATORY DIAGNOSIS

A definitive diagnosis of infection with *Streptococcus 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 >25 white blood cells and <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 examination under oil immersion. If the reaction is positive, the organism will be surrounded by a large capsule.

Several rapid tests for the 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 U.S. 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

Streptococcus pneumoniae is a human pathogen. The reservoir for pneumococci is presumably the nasopharynx of asymptomatic human carriers. There is no animal or insect vector.

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

TRANSMISSION

Transmission of *Streptococcus pneumoniae* occurs as the result of direct person-to-person contact via respiratory droplets, and by autoinoculation in persons carrying the bacteria in their upper respiratory tract. The pneumococcal serotypes most often responsible for causing infection are those most frequently found in carriers. The spread of the organism within a family or household is influenced by such factors as crowding, season, and the presence of upper respiratory infections or pneumococcal disease such as pneumonia or otitis media. The spread of pneumococcal disease is usually associated with increased carriage rates. However, high carriage rates do not appear to increase the risk of disease transmission in households.

TEMPORAL PATTERN

Pneumococcal infections are more common during the winter and in early spring when respiratory diseases are more prevalent.

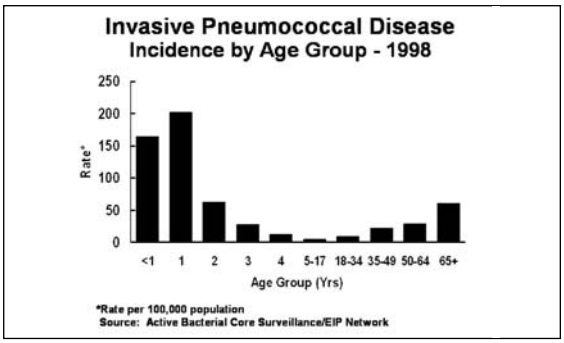
COMMUNICABILITY

The period of communicability for pneumococcal disease is unknown, but presumably transmission can occur as long as the organism appears in respiratory secretions.

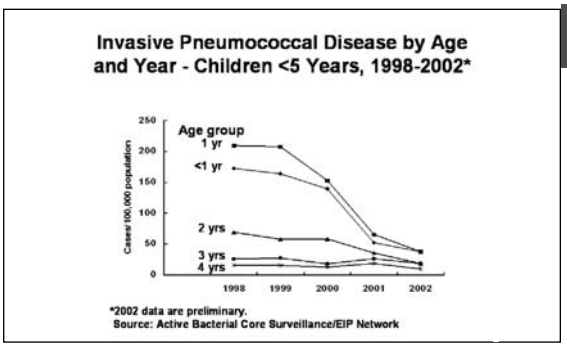
SECULAR TRENDS IN THE UNITED STATES

Estimates of the incidence of pneumococcal disease have been made from a variety of population-based studies. More than 40,000 cases and more than 5,500 deaths from invasive pneumococcal disease (bacteremia and meningitis) are estimated to have occurred in the United States in 2002. More than half of these cases occur in adults who have an indication for pneumococcal polysaccharide vaccine. In addition, there are thousands of cases of non-bacteremic 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 in young children, especially those <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 in persons 5-17 years of age, and increased to 61 per 100,000 population in persons 65 years of age and older.



Data from the Active Bacterial Core Surveillance (ABCs) system suggests that the use of pneumococcal conjugate vaccine is having an impact on the incidence of invasive disease among young children. Preliminary data from 2002 indicate that rates of invasive pneumococcal disease have declined 70%-80% among children <2 years of age, compared to 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.



Children with functional or anatomic asplenia, particularly those with sickle cell disease, and children with HIV infection are at very high risk of invasive disease, with rates in some studies more than 50 times higher than children of the same age without these conditions (*i.e.*, incidence rates of 5,000-9,000 per 100,000 population). Children of certain racial and ethnic groups have increased rates, in particularly children of Alaskan Native, certain American Indian groups, and of African American origin. 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 bacteria).

Children at Increased Risk of Invasive Pneumococcal Disease

- Functional or anatomic asplenia, especially sickle cell disease
- HIV infection
- Alaskan native, Native American, African American
- Daycare attendance

Attendance at a daycare center has also been shown to increase the risk of invasive pneumococcal disease and acute otitis media from 2-3-fold among children <59 months of age.

Pneumococcal Disease Outbreaks

- Outbreaks uncommon
- Generally occur 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 jails and nursing homes. During outbreaks, persons with invasive disease often have underlying illness and may have a high fatality rate.

PNEUMOCOCCAL VACCINES

CHARACTERISTICS

Pneumococcal Polysaccharide Vaccine

Pneumococcal Vaccines

- 1977 14-valent polysaccharide vaccine licensed
- 1983 23-valent polysaccharide vaccine licensed
- 2000 7-valent polysaccharide conjugate vaccine licensed

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 which cause 88% of bacteremic pneumococcal disease. In addition, cross-reactivity occurs for several capsular types which account for an additional 8% of bacteremic disease.

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

The polysaccharide vaccine currently available in the United States (Pneumovax 23, Merck) contains 25 mcg of each antigen per dose and contains 0.25% phenol as a preservative. The vaccine is available in a single dose vial or syringe, and in a 5 dose vial. Pneumococcal vaccine is given by injection, and may be administered either intramuscularly or subcutaneously.

Pneumococcal Conjugate Vaccine

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

The first pneumococcal conjugate vaccine (PCV7) was licensed in the United States in 2000. It includes purified capsular polysaccharide of 7 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 <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.

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 less 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 fall more quickly in persons with certain underlying illnesses.

PPV23 vaccine efficacy studies have resulted in various estimates of clinical effectiveness. Overall, the vaccine is 60%-70% effective in preventing invasive disease. The vaccine appears to be less effective in preventing nonbacteremic pneumococcal pneumonia. 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 infections, it is still recommended for such persons because they are at high risk of developing severe disease.

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 nonvaccine-type organisms have been observed as the result of vaccination.

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

Pneumococcal Conjugate Vaccine

After 4 doses of PCV7 vaccine, >90% of healthy infants develop antibody to all 7 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 with X-ray with consolidation of ≥2.5 centimeters by 73%. Children who received PCV7 had 7% fewer episodes of acute otitis media and underwent 20% fewer tympanostomy tube placements than unvaccinated children. The duration of protection following PCV7 is currently unknown. The effect of PCV7 on nasopharyngeal carriage of pneumococci is not clear at this time.

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

VACCINATION SCHEDULE AND USE

Pneumococcal Polysaccharide Vaccine

Pneumococcal polysaccharide vaccine should be administered rou-

Pneumococcal Polysaccharide Vaccine Recommendations

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

tinely to **all adults 65 years of age and older.** The vaccine is also indicated for **persons aged ≥2 years with a normal immune system who have a chronic illness,** including cardiovascular disease, pulmonary disease, diabetes, alcoholism, cirrhosis, or cerebrospinal fluid leak.

Immunocompromised persons aged ≥2 years 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's 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) should be vaccinated. Persons aged ≥2 years with 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 populations.

If elective splenectomy is being considered, the vaccine should be given at least 2 weeks before the operation. If vaccination prior to splenectomy is not feasible, the vaccine should be given as soon as possible after surgery. Similarly, there should also be a two 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.**

Pneumococcal Conjugate Vaccine

- Routine vaccination of children age <24 months and children 24-59 months with high risk medical conditions
- Doses at 2, 4, 6, months, booster dose at 12-15 months
- Unvaccinated children >7 months require fewer doses

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.

Pneumococcal Conjugate Vaccine

All children <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 <12 months of age, the minimum interval between doses is 4 weeks. Doses given at ≥12 months of age should be separated by at least 8 weeks.

Unvaccinated children 7 months of age and older do not require a full series of 4 doses. The number of doses a child needs to complete the series depends on the child's current age. Unvaccinated

children aged 7-11 months should receive two doses of vaccine, at least 4 weeks apart, followed by a booster dose at age 12-15 months. Unvaccinated children aged 12-23 months should receive two doses of vaccine, at least 8 weeks apart. Previously unvaccinated healthy children aged 24-59 months should receive a single dose of PCV7. Unvaccinated children aged 24-59 months with sickle cell disease, asplenia, HIV infection, chronic illness, or immunocompromising conditions should receive 2 doses of PCV7 separated by at least 8 weeks.

ACIP recommends that healthcare providers consider PCV7 for all children aged 24-59 months, with priority given to children aged 24-35 months, children of Alaskan Native, American Indian or African American descent, and children who attend group daycare (defined as any setting outside the home where a child regularly spends ≥4 hours per week with ≥2 unrelated children under adult supervision).

Pneumococcal Conjugate Vaccine

- Consider for all children aged 24-59 months
- Priority given to children 24-59 months at increase risk:
  - 24-35 months of age
  - Alaskan Native, American Indian, and African American descent
  - attend group child care

PCV7 is not routinely recommended for persons >59 months of age.

Few data are available on the use of PCV7 among children previously vaccinated with PPV23. Children 24-59 months of age who have already received PPV23 and who are at high-risk of invasive pneumococcal disease (sickle cell disease, asplenia, HIV infection or other immunocompromising conditions or chronic diseases) could benefit from the immunologic priming induced by PPV23. ACIP recommends these children receive 2 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 Conjugate Vaccine

- Children aged 25-59 months at high risk 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

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-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.

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

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 five 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 aged 10 years or less at the time of revaccination, including children who received PCV7.

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

Persons at highest risk include all people ≥2 years of age with functional or anatomic asplenia (*e.g.*, sickle cell disease or splenectomy), HIV infection, leukemia, lymphoma, Hodgkins 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 less than 65 years of age at the time of the first dose.

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, from 30% to 50% of vaccinees report pain, swelling, or erythema at the site of injection. These reactions usually persist for less than 48 hours.

Pneumococcal Vaccines Adverse Reactions

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

Local reations are reported more frequently following a second dose of PPV23 vaccine than following the first dose. Moderate **systemic reactions** (such as fever and myalgias) are not common (<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 Conjugate Vaccine

Local reactions following PCV7 occur in 10%-20% of recipients. Fewer than 3% of local reactions are considered to be severe (*e.g.*, tenderness that interferes with limb movement). Local reactions are more common with the fourth dose than with the first 3 doses. In clinical trials of pneumococcal conjugate vaccine, fever >38°C within 48 hours of any dose of the primary series was reported in 15%-24% of children. However, in these studies, whole-cell pertussis vaccine was administer 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 >39°C. No severe adverse events attributable to PCV7 have been reported.

CONTRAINDICATIONS AND PRECAUTIONS TO VACCINATION

For both pneumococcal polysaccharide and conjugate vaccines, a **serious 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.

Pneumococcal Vaccines Contraindications and Precautions

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

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 (2°-8°C [35°-46°F])

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 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. Data from the 2002 Behavioral Risk Factor Surveillance System (BRFSS, a population-based, random-digit-dialed telephone

Pneumococcal Polysaccharide Vaccine Coverage

- Healthy People 2010 goal: 90% coverage for persons ≥65 years
- 2002 BRFSS: 66% of persons ≥65 years of age ever vaccinated
- Vaccination levels lower for black (45%) and Hispanic (44%) persons

survey of the noninstitutionalized U.S. population 18 years of age and older) estimates that 54% of persons 65 years of age or older had ever received pneumococcal polysaccharide, an increase of 18% since the 1995 survey. Vaccination levels increased in all but one state and were significantly lower among black and Hispanic persons than among white persons.

Pneumococcal Polysaccharide Vaccine Missed Opportunities

- >65% of patients with severe pneumococcal disease had been hospitalized within preceding 3-5 years but had not been immunized
- May be administered simultaneously with influenza vaccine

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, clinicians' offices, nursing homes, and other chronic care facilities.

More than two-thirds of the persons who have been hospitalized with serious pneumococcal disease had been admitted to a hospital in the preceding 3 to 5 years. 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 in reducing complications and death associated with pneumococcal disease.

SELECTED REFERENCES

American Academy of Pediatrics. Pneumococcal infections. In: Pickering L, ed. *Red Book: 2003 Report of the Committee on Infectious Diseases.* 26th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2003:490-500.

Black S, Shinefield HR, Fireman B, et al. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. *Pediatr Infect Dis J* 2000;19:187-95.

Butler JC, Breiman RF, Campbell JF, et al. Pneumococcal polysaccharide vaccine efficacy: an evaluation of current recommendations. *J Am Med Assoc* 1993;270:1826-31.

CDC. Active Bacterial Core Surveillance. Available at http://www.cdc.gov/ncidod/dbmd/abcs/. Accessed January 7, 2004.

CDC. Prevention of pneumococcal disease among infants and young children using a pneumococcal conjugate vaccine. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2000;49(RR-9):1-35.

CDC. Prevention of pneumococcal disease. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 1997;46(RR-8):1-24.

CDC. Public health and aging: influenza vaccination coverage among adults aged >50 years and pneumococcal vaccination coverage among adults aged >65 years - United States, 2002. *MMWR* 2003;(52);987-92.

Jackson LA, Benson P, Sneller VP, et al. Safety of revaccination with pneumococcal polysaccharide vaccine. *J Am Med Assoc* 1999;281:243-8.

Robinson KA, Baughman W, Rothrock G. Epidemiology of invasive Streptococcus pneumoniae infections in the United States, 1995-1998. Opportunities for prevention in the conjugate vaccine era. *J Am Med Assoc* 2001;285:1729-35.

Whitney CG. The potential of pneumococcal conjugate vaccines for children. *Pediatr Infect Dis J* 2002;21:961-70.

Whitney CG, Farley MM, Hadler J, et al. Decline in invasive pneumococcal disease after introduction of protein-polysaccharide conjugate vaccine. *N Eng J Med* 2003;348:1737-46.

Whitney CG, Shaffner W, Butler JC. Rethinking recommendations for use of pneumococcal vaccines in adults. *Clin Infect Dis* 2001;33:662-75.

Meningococcal disease is an acute, potentially severe illness caused by the bacteria *Neisseria meningitidis*. Illness believed to be meningococcal disease was first reported in the sixteenth century. The first definitive description of the disease was by Vieusseux in Switzerland in 1805. The bacteria 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 estimated meningococcal disease was the cause of 171,000 deaths worldwide in 2000.

The first monovalent (group C) polysaccharide vaccine was licensed in the U.S. in 1974. The current quadrivalent vaccine was licensed in 1978. Meningococcal conjugate vaccine is licensed in Europe, and has had a major impact on the incidence of type C meningococcal disease in the United Kingdom. A meningococcal conjugate vaccine may be available in the United States in the future.

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

NEISSERIA MENINGITIDIS

Neisseria meningitidis, or meningococcus, is an aerobic gram-negative diplococcus, closely related to *Neisseria gonorrhea*, 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 which enable the bacteria to interact with the host cells, as well as 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 comprise the main surface antigens of the organism.

Meningococci are classified using serological methods based on the structure of the polysaccharide capsule. Thirteen antigenically and chemically distinct polysaccharide capsules have been described. Some strains, often those found to cause asymptomatic nasopharyngeal carriage, are not groupable, and do not have a capsule. Almost all invasive disease is caused by one of five serogroups: A, B, C, Y, and W-135. The relative importance of each serogroup depends on geographic location, as well as other factors, such as age. For instance, serogroup A is a major cause of disease in sub-Saharan Africa, but is rarely isolated in the United States.

Neisseria meningitidis

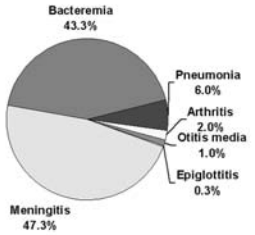
- Aerobic gram-negative bacteria
- At least 13 serogroups based on characteristics of the polysaccharide capsule
- Most invasive disease caused by serogroups A, B, C, Y, and W-135
- Relative importance of serogroups depends on geographic location and other factors (e.g. age)

Meningococci are further classified on the basis of certain outer membrane proteins. Molecular subtyping using specialized laboratory techniques (e.g., pulsed-field 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

Neisseria meningitidis* Clinical Manifestations



*1992-1996 data

Meningococcal Meningitis

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

Meningococcemia

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

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 (<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 URI may be a contributing factor.

CLINICAL FEATURES

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

Meningitis is the most common presentation of invasive meningococcal disease and results from hematogenous dissemination of the organism. Meningeal infection is similar to other forms of acute purulent meningitis, with sudden onset of fever, headache, and stiff neck, often accompanied by other symptoms, such as nausea, vomiting, photophobia (eye sensitivity to light), and altered mental status. Meningococci can be isolated from the blood in up to 75% of persons with meningitis.

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.

Less common presentations of meningococcal disease include pneumonia (5%-15% of cases), arthritis (2%), otitis media (1%), and epiglottitis (<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%. Up to 20% of survivors have permanent sequelae, such as hearing loss, neurologic damage, or loss of a limb.

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.

***Neisseria meningitidis* Medical Management**

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

EPIDEMIOLOGY

OCCURRENCE

Meningococcal disease occurs worldwide in both endemic and epidemic form.

RESERVOIR

Humans are the only natural reservoir of meningococcus. Up to 10% of adolescents and adults are asymptomatic transient carriers of *N. meningitidis*, most of which are not pathogenic (i.e, strains that are not groupable).

Meningococcal Disease Epidemiology

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

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.

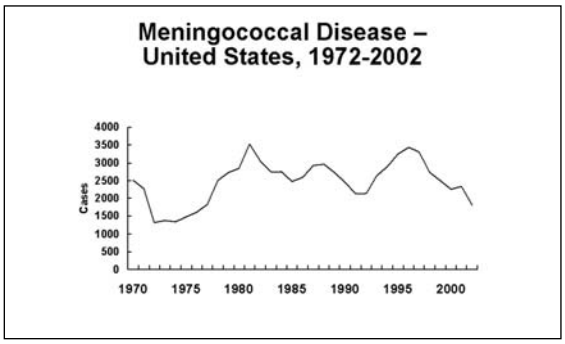
COMMUNICABILITY

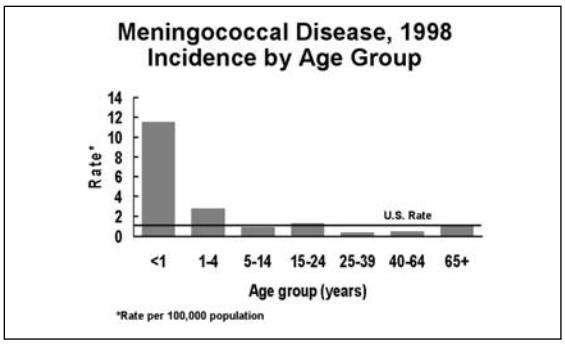
The communicability of *N. meningitidis* is generally limited. In studies of households in which a case of meningococcal disease has occurred, only 3%-4% of households had secondary cases. Most households had only one secondary case. Estimates of the risk of secondary transmission are generally 2-4 per 1000 household

members at risk. However, this risk is 500-800 times that of the general population.

SECULAR TRENDS IN THE UNITED STATES

Approximately 2,500 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 2002, an estimated 150 deaths due to meningococcal disease occurred in the United States. **Infants <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. 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 cases 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, in 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 varies by age group. In 2001, 65% of cases among infants aged <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 or Y, respectively.

Meningococcal Disease in the United States

- Distribution of cases by serogroup varies by time and age group
- In 1996-2001:
  - 31% serogroup B
  - 42% serogroup C
  - 21% serogroup Y
  - 65% of cases among children <1 year of age due to serogroup B

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.

Neisseria meningitidis
Risk factors for invasive disease

- Host factors
  - Terminal complement pathway deficiency
  - Asplenia
  - Genetic risk factors
- Exposure factors
  - Household exposure
  - Demographic and socioeconomic factors and crowding
  - Concurrent upper respiratory tract infection
  - Active and passive smoking

Family members of a person with meningococcal disease are at increased risk. Antecedent viral infection, household crowding, and both active and passive smoking also are associated with increased risk for meningococcal disease. In the United States, blacks and persons of low socioeconomic status have been consistently at higher risk for meningococcal disease. 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 2 fatal cases, have been reported among microbiologists. Cases have occurred among persons who work with *N. meningitidis* isolates rather than patient specimens.

Recent 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 people of similar age.

In the United States, **meningococcal outbreaks** account for <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 serogroup Y and B organisms 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.

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

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 POLYSACCHARIDE VACCINE

CHARACTERISTICS

The first meningococcal polysaccharide vaccine (MPV) was licensed in the United States in 1974. The current quadrivalent A, C, Y, W-135 polysaccharide vaccine (Menomune, manufactured by Aventis Pasteur) was licensed in 1978, and is the only formulation currently available in the United States. Each dose consists of 50 µg of each of the four purified bacterial capsular polysaccharides. The vaccine contains lactose as a stabilizer.

Meningococcal Polysaccharide Vaccine

- Menomune (Aventis Pasteur)
- Quadrivalent polysaccharide vaccine (A, C, Y, W-135)
- Not effective in children <18 months
- Schedule: 1 dose with revaccination in 2-5 years (if indicated)

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.

IMMUNOGENICITY AND VACCINE EFFICACY

The characteristics of MPV are similar to other polysaccharide vaccines (e.g., pneumococcal polysaccharide). The vaccine is not effective among children younger than 18 months of age. The response to the vaccine is typical of a T-independent antigen, with an age-dependent response, and poor immunogenicity in children <2 years of age. In addition, no boost in antibody titer occurs with repeated doses, the antibody which is produced is relatively low-affinity IgM, and "switching" from IgM to IgG production is poor.

Polysaccharide Vaccines

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

A protective level of antibody is usually achieved within 7-10 days of vaccination. Among infants and children <5 years of age, measurable levels of antibodies against serogroup A and C polysaccharides decrease substantially during the first 3 years following a single dose of vaccine. In healthy adults, antibody levels also decrease, but antibodies are detectable as long as 10 years after vaccination. Although vaccine-induced protection likely persists in school-aged children and adults for at least 3 years, the efficacy of the group A vaccine in children <5 years of age may decrease markedly within this period. In one study, efficacy declined from >90% to <10% three years after vaccination among children who were aged <4 years when vaccinated. Efficacy was 67% among children who were >4 years of age at vaccination.

Meningococcal Polysaccharide Vaccine Schedule

- Single 0.5-mL dose
- Subcutaneous administration
- Can be administered at the same time as other vaccines
- Protective level of antibody is usually achieved within 7-10 days of vaccination

Meningococcal Polysaccharide Vaccine Recommendations

- Not recommended for routine vaccination of civilians
- Recommended for certain high-risk persons:
  - Terminal complement deficiency
  - Functional or anatomic asplenia
  - Certain laboratory workers
  - Travelers to and U.S. citizens residing in countries in which N. meningiditis is hyperendemic or epidemic (e.g., African meningitis belt)

Meningococcal Endemic Areas 2000

Meningococcal Polysaccharide Vaccine Recommendations

- Control of outbreaks
- Outbreak definition:
  - 3 or more confirmed or probable 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

VACCINATION SCHEDULE AND USE

For both children and adults, MPV is administered **subcutaneously 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 MPV is not recommended because of its relative ineffectiveness in children <2 years of age (the age group with the highest risk for sporadic disease) and because of its relatively short duration of protection.

Vaccination with MPV is recommended for certain high-risk groups, including persons who have **terminal complement component deficiencies** and those who have **functional or anatomic asplenia.** Research, industrial, and clinical **laboratory personnel** who are exposed routinely to *N. meningitidis* in solutions that may be aerosolized also should be considered for vaccination. Laboratory workers should also follow appropriate laboratory precautions (biosafety level 2), particularly when working with isolates.

Vaccination with MPV may benefit **travelers to and U.S. citizens residing in countries in which *N. meningitidis* is hyperendemic or epidemic,** particularly if contact with the local population will be prolonged. Recurrent epidemics of meningococcal disease occur 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). As a result, vaccination is recommended for travelers visiting the region during this time. Information concerning geographic areas for which vaccination is recommended can be obtained from the CDC Travelers Health website at http://www.cdc.gov/travel/.

Meningococcal polysaccharide vaccine is recommended for use in **control of meningococcal outbreaks.** An outbreak is defined by the occurrence of three or more confirmed or probable cases of meningococcal disease during a period of <3 months, with a resulting primary attack rate of ≥10 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.

College freshmen, particularly those living in dormitories or residence halls, are at modestly increased risk for meningococcal disease compared with persons the same age who are not attending college. However, **ACIP does not recommend routine MPV vaccination of all college students,** freshmen college students, or students who reside in dormitories. ACIP recommends that providers of medical care to incoming and current college freshmen, particularly those who plan to or already live in dormitories and residence halls, should, during routine medical care, inform these students and their parents about meningococcal disease and the benefits of vaccination. ACIP does not recommend that the level of increased risk among freshmen warrants any specific changes in living situations for freshmen. College freshmen who want to reduce their risk for meningococcal disease should either be administered vaccine by the provider or directed to a site where vaccine is available. Refer to the ACIP statement on this topic at http://www.cdc.gov/mmwr/PDF/rr/rr4907.pdf for more information.

Meningococcal Polysaccharide Vaccine for College Students

- ACIP does not recommend routine vaccination for college students
- Inform students about meningococcal disease and benefits of vaccination
- Administer if requested or direct to site where vaccine is available (e.g., college health service)

REVACCINATION

Revaccination may be indicated for persons at high risk for infection (*e.g.,* persons residing in areas in which disease is epidemic), particularly for children who were first vaccinated when they were <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 has not been determined, antibody levels rapidly decline in 2-3 years, and if indications still exist for vaccination, revaccination may be considered 3-5 years after receipt of the first dose.

Continued attendance of college, or continued residence in a college dormitory is not an indication for revaccination in the absence of another indication (such as asplenia).

Meningococcal Polysaccharide Vaccine Revaccination

- Revaccination may be indicated for persons at high risk for infection*
- Consider revaccination of children first vaccinated when they were <4 years of age after 2–3 years if they remain at high risk
- The need for revaccination of older children and adults has not been determined
- If indications still exist for vaccination, revaccination may be considered 3–5 years after first dose

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

ADVERSE REACTIONS FOLLOWING VACCINATION

Adverse reactions to MPV 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 5%-10% of recipients. Systemic reactions, such as headache and malaise are reported in 2%-5% of recipients, and low grade fever occurs in up to 3% of vaccinees. Severe reactions to polysaccharide meningococcal vaccine are uncommon.

All serious adverse events that occur after receipt of any vaccine should be reported to the Vaccine Adverse Events Reporting System (VAERS). See the VAERS website at http://www.vaers.org

Meningococcal Polysaccharide Vaccine Adverse Reactions

- Local reactions (erythema, pain) for 1-2 days
- Low grade fever in <2% of children, less commonly in older persons
- Severe reactions rare

Meningococcal Polysaccharide Vaccine Contraindications and Precautions

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

for information on reporting.

CONTRAINDICATIONS AND PRECAUTIONS TO VACCINATION

A **severe allergic (anaphylactic) reaction** to a vaccine component or following a prior dose of meningococcal polysaccharide 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. Pregnancy, breastfeeding, and immunosuppression are not contraindications to vaccination.

VACCINE STORAGE AND HANDLING

MPV should be shipped in insulated containers to prevent exposure to freezing temperature. Vaccine should be stored at refrigerator temperature (2-8° centigrade [35-46° Fahrenheit]). The vaccine must not be exposed to freezing temperature.

Single dose vials of MPV must be used within 30 minutes of reconstitution. Multidose vials must be discarded 35 days after reconstitution.

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, daycare 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). Because the rate of secondary disease for close contacts is highest during the first few days after onset of disease in the index patient, antimicrobial chemoprophylaxis should be administered as soon as possible - ideally within 24 hours after identification of the index patient. Chemoprophylaxis administered >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 may unnecessarily delay institution of this preventive measure.

Rifampin, ciprofloxacin, and ceftriaxone are all 90%-95% effective in reducing nasopharyngeal carriage of *N. meningitidis* and are all acceptable alternatives for chemoprophylaxis. Systemic antimicrobial therapy of meningococcal disease with agents other than ceftriaxone or other third-generation cephalosporins may 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. Information on dosage, duration, and route of administration are available in the meningococcal vaccine ACIP statement at www.cdc.gov/mmwr/PDF/rr/rr4907.pdf.

SELECTED REFERENCES

Active Bacterial Core Surveillance (ABCs) 2001 provisional meningococcal surveillance report. Available at http://www.cdc.gov/ncidod/dbmd/abcs/. Accessed December 30, 2003.

American Academy of Pediatrics. Meningococcal Disease. In: Pickering L ed. *Red Book: 2003 Report of the Committee on Infectious Diseases*. 26th ed. Elk Grove Village, IL: American Academy of Pediatrics, 2003: 430-6.

Baltimore RS. Meningococcal infections. In: Evans AS and Brachman PS, eds. *Bacterial infections of humans. Epidemiology and control*. 3rd ed. New York, NY: Plenum Medical Book Company; 1998: 459-79.

CDC. Prevention and control of meningococcal disease and meningococcal disease and college students. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2000;49(RR-7):1-22.

CDC. Laboratory-acquired meningococcal disease - United States, 2000. *MMWR* 2002;51:141-4.

Granoff DM, Feavers IM, Borrow R. Meningococcal vaccine. In: Plotkin SA and Orenstein WA, eds. *Vaccines*. 4th ed. Philadelphia, PA: Saunders; 2003: 959-87.

Harrison LH, Pass MA, Mendelsohn AB, et al. Invasive meningococcal disease in adolescents and young adults. *J Am Med Assoc* 2001;286(6):694-9.

Jodar L, Feavers IM, Salisbury D, Granoff DM. Development of vaccines against meningococcal disease. *Lancet* 2002;359(9316):1499-1508.

Morley SL, Pollard AJ. Vaccine prevention of meningococcal disease, coming soon? *Vaccine* 2002;20:666-87.

Rosenstein NE, Perkins BA, Stephens DS, et al. Meningococcal disease. *New Eng J Med* 2001;344(18):1378-88.

Van Deuren M, Brandtzaeg, Van der Meer JWM. Update on meningococcal disease with emphasis on pathogenesis and clinical management. *Clin Micro Rev* 2000;13(1):144-66.

Smallpox is an acute infectious disease caused by the variola virus. Smallpox is believed to have emerged in human populations about 10,000 BCE. A description of smallpox first appeared in a Chinese text in the 4th century. The name variola was first used during the 6th century and is a derivative of the Latin *varius*, meaning spotted or *varus*, meaning pimple. The first efforts to prevent smallpox occurred in China and India in the 8th century, and involved intentional inoculation of a susceptible person with pustular or scab material from a person with smallpox. The term smallpox was first used in Europe in the 15th century to distinguish variola from the great pox (syphilis). In 1796 Edward Jenner demonstrated that smallpox could be prevented by inoculation of a person with material from a cowpox lesion, which led to the first smallpox vaccine. The last case of smallpox in the United States was reported in Texas in 1949. In 1966 the World Health Organization initiated an intensified global smallpox eradication program. The last indigenous case of smallpox on earth occurred in Somalia in October 1977. The World Health Assembly officially certified the global eradication of smallpox in May 1980.

Smallpox

- First described in Chinese text in 4th century AD
- Vaccine developed in late 18th century
- Last case in U.S. in 1949
- Last indigenous case on earth in 1977

VARIOLA AND OTHER ORTHOPOXVIRUSES

Smallpox is caused by variola virus. Variola virus belongs to the genus Orthopoxvirus, family Poxviridae. Poxviruses are large brick-shaped viruses with a double stranded DNA genome. They are different from most other DNA viruses in that they replicate in the cytoplasm of the cell rather than in the nucleus. To do this, they produce a variety of proteins not produced by other DNA viruses (*e.g.*, herpes virus). Four orthopoxviruses are known to infect humans: variola, vaccinia, cowpox, and monkeypox. Variola virus infects only humans in nature, although primates and other animals have been infected in a laboratory. Vaccinia, cowpox, and monkeypox viruses can infect both humans and other animals in nature.

Variola Virus

- Orthopoxvirus
- Infects only humans in nature
- May remain viable in crusts for years at room temperature
- Rapidly inactivated by UV light, chemical disinfectants

In laboratory experiments, 90% of aerosolized variola virus is inactivated within 24 hours. In the presence of ultraviolet light, this percentage would be even greater. In temperate climates, crusts from the skin lesions from smallpox patients, in which the virus is contained in a fibrin matrix, can retain viable virus for several years when held at room temperature. The virus survives longer at low temperature and humidity than at higher temperature or humidity. All poxviruses are rapidly inactivated by exposure to ultraviolet light, and chemical disinfectants such as bleach or Lysol®.

Some persons infected with variola major virus have particularly severe illnesses. This suggests that there could be differences in the virulence of strains of the virus. However, no laboratory test has been devised that correlates with virulence in humans. Physiologic factors in the host are probably the more important determinant of severity of the illness.

Smallpox vaccine contains vaccinia virus, not variola virus. Vaccinia is rarely isolated from animals outside the laboratory.

There are multiple strains of vaccinia virus that have different levels of virulence for humans and animals. Vaccinia virus can also be genetically engineered to accept DNA and express other antigens, and has been used as a vector in laboratory experiments. Cowpox virus was probably the virus that Edward Jenner originally used as a vaccine for smallpox. The virus has many natural hosts, including cows, rodents, cats, elephants, and is found in nature primarily in Europe. Monkeypox infects primates, anteaters and squirrels, and is found primarily in western and central Africa.

PATHOGENESIS

Smallpox Pathogenesis

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

Variola virus infection is initiated when the virus comes into contact with the oropharyngeal or respiratory mucosa. Virus multiplication then occurs in regional lymph nodes. An asymptomatic viremia develops 3 or 4 days after infection which is followed by virus replication, probably in the bone marrow, spleen, and lymphatics. A second viremia begins about 8-10 days after infection and is followed by the first symptoms of illness (prodromal stage), fever and toxemia. The virus localizes in small blood vessels of the dermis and in the oral and pharyngeal mucosa. In the skin this results in the characteristic maculopapular rash, which evolves into vesicles, then pustules.

CLINICAL FEATURES

Smallpox Clinical Presentations

- Variola major
  - Severe illness
  - Case fatality rate of ≥30%
- Variola minor
  - Less severe
  - Case fatality of ≤1%

Two clinical forms of smallpox have been described. While both forms are caused by variola virus, they are caused by different strains of the virus distinguishable by specific biologic properties (such as growth characteristics in cell culture and DNA structure). **Variola major** is the severe form of smallpox, with a more extensive rash, higher fever, and a greater degree of prostration. Variola major has a case fatality rate of 30% or more. The last case of variola major occurred in Bangladesh in 1975. **Variola minor** was first described in South Africa and the United States in the late 19th Century. Variola minor is a much less severe disease, with a case fatality rate of 1% or less. Variola minor was endemic in some countries of Europe and of North and South America, and in many parts of Africa. The last case of variola minor occurred in Somalia in October 1977, and was the last case of indigenous smallpox on earth.

Clinical Presentations of Variola Major

- Ordinary (≥90% of cases in unvaccinated people)
- Modified (mild; occurs in previously vaccinated people)
- Flat (uncommon; usually fatal)
- Hemorrhagic (uncommon; usually fatal)

There are **four principal clinical presentations of variola major**, based on the Rao classification (1972). The relative vigor of the immune response to the infection probably determined the clinical presentation of the infection. The classification is based on the nature and evolution of the lesions: ordinary (most frequent); modified (mild and occurring in previously vaccinated persons); flat; and hemorrhagic. Flat and hemorrhagic smallpox are severe, uncommon forms and are usually fatal. In addition, variola sine eruptione (smallpox without rash) is a febrile illness occurring after the usual incubation period. It is seen generally in vaccinated persons and can be confirmed only by antibody studies or, rarely, by virus isolation. Subclinical (asymptomatic) infections with variola

virus also occurred, but was not believed to be common.

The **incubation period** of smallpox averages 12 days, with a range of 7 to 17 days. During this period the patient is well. The **prodrome** or pre-eruptive stage of the illness then starts abruptly, with fever (usually 101°-104°F), malaise, headache, muscle pain, prostration, and often nausea and vomiting and backache. The person usually appears quite ill. The prodrome usually lasts 2-4 days. The person is not infectious until the end of the prodrome, when lesions develop in the mouth.

Smallpox Prodrome

- Incubation period 12 days (range 7-17 days)
- Prodrome
  - abrupt onset of fever ≥101°F
  - malaise, headache, muscle pain, nausea, vomiting, backache
  - lasts 2-4 days
  - not infectious until lesions develop in mouth

ORDINARY SMALLPOX

Ninety percent or more of smallpox cases among unvaccinated persons are of the ordinary-type. The prodromal stage is of varying severity. By the third or fourth day of illness the temperature usually falls and the patient feels somewhat better. At this point the rash appears. The rash appears first as an **enanthem** - minute red spots on the tongue and oral and pharyngeal mucosa, about 24 hours before the appearance of rash on the skin. Lesions in the mouth and pharynx enlarge and ulcerated quickly, releasing large amounts of virus into the saliva about the time the cutaneous rash first becomes visible. Virus titers in saliva are highest during the first week of illness, corresponding with the period during which patients are most infectious.

Smallpox Rash

- Enanthem (mucous membrane lesions) appears approx. 24 hours before skin rash
- Minute red spots on the tongue and oral/pharyngeal mucosa
- Lesions enlarge and ulcerate quickly
- Virus titers in saliva highest during first week of exanthem

The **exanthem** (skin rash) usually appears 2-4 days after the onset of fever as a few macules (known as "herald spots") on the face, particularly on the forehead. Lesions then appear on the proximal portions of the extremities, then spread to the distal extremities and the trunk. Usually the rash appears on all parts of the body within 24 hours.

Smallpox Rash

- Exanthem (skin rash) appears 2-4 days after onset of fever
- First appears as macules, usually on the face
- Lesions appear on proximal extremities, spread to distal extremities and trunk

By the second or third day of the rash, the macules become raised papules. By the third or fourth day the lesions become vesicular, containing first an opalescent fluid, which then becomes opaque and turbid within 24-48 hours. The skin lesions of smallpox typically are surrounded by a faint erythematous halo. The distended vesicles often have a central depression or dimple of varying size, referred to as "**umbilication**." Umbilication often persists into the pustular stage, but as the lesion progresses it usually becomes flattened because of adsorption of fluid. Umbilication is less common in other vesicular or pustular rash illnesses, particularly in varicella.

Smallpox Rash Evolution

Stage	Days after Rash Onset
Macules	0-1
Papules	2-3
Vesicles	3-5
Pustules	6-12
Crusts	13-20
All crusts separated	21-28

By the sixth or seventh day, all the skin lesions are pustules. Between 7 and 10 days the pustules mature and reach their maximum size. The pustules are sharply raised, typically round, tense, and firm to the touch. **The pustules are deeply embedded in the dermis, giving them the feel of a small bead in the skin**. Fluid is slowly absorbed from the pustules and by the end of the second week the pustules begin to form a crust. During the third week the crusts separate, leaving depigmented skin which eventually become pitted scars. Fever usually rises again by the seventh or

Smallpox Rash

- Vesicles often have a central depression ("umbilication")
- Pustules raised, round, firm to the touch, deeply embedded in the skin
- Lesions in any one part of the body are in same stage of development
- Most dense on face and distal extremities (centrifugal distribution)
- Lesions on palms and soles (≥50% of cases)

eighth day of the illness and continues to remain high throughout the vesicular and pustular stages, until crusts have formed over all the lesions.

The rash usually develops as a single crop. Consequently, **lesions in a particular part of the body are at about the same stage of development**, although they may be different sizes. The distribution of the rash is centrifugal: most dense on the face; more dense on the extremities than on the trunk; and on the extremities, more dense on the distal parts than on the proximal. The palms of the hands and soles of the feet are involved in the majority of cases.

In general, the severity of the clinical picture parallels the extent of the rash. In some cases, the pustular skin lesions on the extensor surfaces of the extremities and face are so numerous they became confluent. Patients with confluent smallpox often remain febrile and toxic even after scabs have formed over all the lesions. In one case series the case-fatality rate in confluent smallpox was 62%.

MODIFIED SMALLPOX

Modified Smallpox

- Occurs in previously vaccinated persons
- Prodrome may be less severe
- No fever during evolution of rash
- Skin lesions evolve more quickly
- Rarely fatal
- More easily confused with chickenpox

Modified smallpox refers to the character of the eruption and the rapidity of it's development. This form of smallpox occurs mostly in previously vaccinated patients. The prodromal illness occurs but may be less severe than in ordinary type smallpox. Fever during evolution of the rash is usually absent. The skin lesions tend to evolve more quickly, are more superficial, and may not show the uniformity characteristic of more typical smallpox. The lesions are often few in number, but even when they are numerous, or even confluent, they usually evolve rapidly. Modified smallpox is rarely, if ever, fatal. This form of variola major is more easily confused with chickenpox.

FLAT (MALIGNANT) SMALLPOX

Flat Smallpox

- Severe prodrome
- Fever remains elevated throughout course of illness
- Extensive enanthem
- Skin lesions soft and flat, contain little fluid
- Most cases fatal

Flat-type smallpox is so called because the lesions remain more or less flush with the skin at the time when raised vesicles form in ordinary-type smallpox. It is not known with certainty why some persons develop this type of disease. In a large series of persons hospitalized with smallpox in India, flat-type smallpox accounted for 5%-10% of cases, and the majority (72%) were in children. The prodrome is severe and lasts 3-4 days. Constitutional symptoms are severe and continue after the appearance of the rash. The fever remains elevated throughout and the patient has severe toxemic symptoms. The rash on the tongue and palate is usually extensive. The skin lesions mature very slowly. By the seventh or eighth day the lesions are flat and appear to be buried in the skin. Unlike ordinary-type smallpox the vesicles contain very little fluid and do not appear umbilicated. The lesions are soft and velvety to the touch, and may contain hemorrhages. Respiratory complications are common. The prognosis for flat-type smallpox is grave and most cases are fatal.

HEMORRHAGIC SMALLPOX

Hemorrhagic smallpox is a severe and uncommon form of smallpox that is accompanied by extensive bleeding into the skin, mucous membranes and gastrointestinal tract. In the large Indian series, hemorrhagic disease occurred in about 2% of hospitalized patients; the majority of cases were among adults, and pregnant women appear to be at increased risk. The prodromal stage, which can be prolonged, is characterized by fever, intense headache and backache, restlessness, a dusky flush or sometimes pallor of the face, extreme prostration, and toxicity. There is little or no remission of fever throughout the illness. Hemorrhagic manifestations can occur early or late in the course of the illness. In the early, or fulminating form hemorrhagic manifestations appear on the second or third day as subconjunctival bleeding, bleeding from the mouth or gums and other mucous membranes, petechiae in the skin, epistaxis, and hematuria. Death often occurs suddenly between the fifth and seventh days of illness, when only a few insignificant maculopapular cutaneous lesions were present. In patients who survive for 8-10 days the hemorrhages appear in the early eruptive period, and the rash is flat and does not progress beyond the vesicular stage.

Hemorrhagic Smallpox

- Prolonged severe prodrome
- Fever remains elevated throughout course of illness
- Early or late hemorrhagic signs
- Bleeding into skin, mucous membranes, GI tract
- Usually fatal

VARIOLA SINE ERUPTIONE AND SUBCLINICAL INFECTION

Febrile illness sometimes occurs among vaccinated contacts of cases of smallpox, with the sudden onset of temperature of about 39°C, headache and sometimes backache. The attack often subsides within 48 hours and the temperature returns to normal. Although these symptoms could be caused by other infections, laboratory investigation may show a significant increase in variola antibody following such an attack. There is evidence of true subclinical infection with variola major virus (*i.e.*, serologic evidence of infection with no symptoms), typically in recently vaccinated household contacts of smallpox cases. Persons with subclinical infections have not been shown to transmit the infection to contacts.

COMPLICATIONS

Secondary bacterial infection of the skin is a relatively uncommon complication of smallpox. When this occurred, the fever usually remained elevated. **Arthritis** occurs in up to 2% of cases, most commonly in children. **Respiratory complications** (*e.g.*, bronchitis, pneumonitis, or pneumonia) sometimes develop on about the eighth day of the illness, and can be either viral or bacterial in origin. **Encephalitis** occasionally occurs that is indistinguishable from the acute perivascular demylination observed as a complication of infection due to vaccinia, measles, and varicella.

In fatal cases, **death** usually occurs between the tenth and sixteenth days of the illness. The cause of death from smallpox is not clear, but the infection is now known to involve multiple organs.

Smallpox Complications

- Bacterial infection of skin lesions
- Arthritis
- Respiratory
- Encephalitis
- Death
  - –30% overall for ordinary smallpox
  - –40%-50% for children <1 year
  - –>90% for flat and hemorrhagic smallpox

Circulating immune complexes, overwhelming viremia, or an uncontrolled immune response may be contributing factors. The overall case fatality rate for ordinary-type smallpox is about 30%. However, the fatality rate for children <1 year of age is 40%-50%. The fatality rate for flat-type and hemorrhagic smallpox is ≥90%. The case fatality rate for variola minor is 1% or less.

Sequelae of smallpox includes scarring, which is most common on the face, blindness resulting from corneal ulceration and scarring, and limb deformities due to arthritis and osteomyelitis. There is no evidence of chronic or recurrent infection with variola virus.

DIFFERENTIAL DIAGNOSIS

Differential Diagnosis

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

The disease that most closely resembles smallpox is varicella (chickenpox). **The most important differentiating feature between smallpox and varicella, as well as other rash illnesses is the presence of a prodrome fever and other symptoms before rash onset.** A person with smallpox will have a severe, febrile prodrome that begins 1-4 days before the onset of the rash. The fever is high, usually 102° - 104°F but always at least 101°F. Most children with varicella have a short, mild prodrome, or no prodrome at all before onset of the rash, and have little or no fever before rash onset. Adults, who may develop more severe varicella, are more likely to have fever or other symptoms before rash onset. **If there is no history of a febrile prodrome, smallpox is not likely.** In addition to fever, the prodrome of smallpox is associated with one or more additional symptoms, such as prostration, headache, backache, chills, abdominal pain or vomiting. Patients are frequently too ill to engage in normal activities and typically confine themselves to bed.

Differential Diagnosis

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

Another important differentiating feature of smallpox and varicella is the appearance, evolution, and distribution of the rash. Although there may be some overlap in the appearance of the lesions, particularly early after rash onset, classic smallpox looks very different than varicella. Smallpox lesions are deep in the dermis, and feel hard to the touch described as feeling like a pea under the skin They are round and well circumscribed. As they evolve they may become confluent or umbilicated. The varicella rash is superficial, and the lesions appear to be delicate, and not as well circumscribed. Confluence and umbilication are uncommon in varicella. Smallpox rash lesions appear in a single crop and lesions on any part of the body are in the same stage of development. Lesions are more dense on the extremities than on the trunk and often involve the palms and soles (i.e., centrifugal distribution). In contrast, the rash of varicella appears in several crops, so papules, vesicles, and crusts are seen simultaneously on the same part of the body and new lesions continue to appear for several days. Lesions are typically more dense on the trunk than on the extremities. In severe cases of varicella, rash distribution may not be a useful differentiating feature and rash may occur everywhere on the body including the palms and soles.

Differential Diagnosis

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

For the first 2-3 days the smallpox rash is maculopapular. At this stage of the illness smallpox could be confused with other febrile illnesses with maculopapular rash, such as measles and rubella, and other evolving vesicular rashes including varicella

Other common conditions that might be confused with smallpox are summarized in the table (see below). As the United States re-institutes smallpox vaccination, at least in limited groups, vaccinia vaccine adverse reactions causing generalized vesicular rashes (generalized vaccinia and eczema vaccinatum) should be considered among persons with a history of recent smallpox vaccination or contact close with a vaccinee. In addition there are exceedingly rare causes, such as rickettsial pox and monkeypox. A small percentage of smallpox cases present with hemorrhagic smallpox or a flat-type rash. Both variants are highly lethal. Hemorrhagic smallpox can be mistaken for meningococcemia.

Common Conditions that Might be Confused with Smallpox

Condition	Clinical Clues
Varicella (primary infection with varicella-zoster virus)	Most common in children <10 years; children usually do not have a viral prodrome
Disseminated herpes zoster	Immunocompromised or elderly persons; rash looks like varicella, usually begins in dermatomal distribution
Impetigo *(Streptococcus pyogenes, Staphylococcus aureus)*	Honey-colored crusted plaques with bullae are classic but may begin as vesicles; regional not disseminated rash; patients generally not ill
Drug eruptions	Exposure to medications; rash often generalized
Contact dermatitis	Itching; contact with possible allergens; rash often localized in pattern suggesting external contact
Erythema multiforme minor	Target, "bull's eye", or iris lesions; often follows recurrent herpes simplex virus infections; may involve hands & feet (including palms & soles)
Erythema multiforme (incl. Stevens Johnson Syndrome)	Major form involves mucous membranes & conjunctivae; may be target lesions or vesicles
Enteroviral infection esp. Hand, Foot and Mouth disease	Summer & fall; fever & mild pharyngitis 1-2 days before rash onset; lesions initially maculopapular but evolve into whitish-grey tender, flat often oval vesicles; peripheral distribution (hands, feet, mouth, or disseminated)
Disseminated herpes simplex	Lesions indistinguishable from varicella; immunocompromised host
Scabies; insect bites (incl. fleas)	Itching is a major symptom; patient is not febrile & is otherwise well
Molluscum contagiosum	May disseminate in immunosuppressed persons

CDC has developed criteria that can be used to evaluate suspected smallpox cases and to categorize patients into high, moderate or low risk for smallpox using major and minor diagnostic criteria. There are 3 major smallpox criteria:

1. febrile prodrome (fever $\geq 101^{o}$F) 1-4 days before rash onset and at least one of the following systemic complaints: prostration, headache, backache, chills, vomiting or abdominal pain;
2. rash lesions are deep in the skin, firm or hard to the touch, round and well circumscribed, and may become umbilicated or confluent as they evolve;
3. on any one part of the body all the lesions are in the same stage of development (i.e., all are vesicles or all are pustules).

Smallpox Major Criteria

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

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

Smallpox Minor Criteria

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

Risk of Smallpox by Clinical History and Examination

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

Laboratory Confirmation

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

There are five minor smallpox criteria:

1. the distribution of the rash is centrifugal (*i.e.*, the greatest concentration of lesions is on the face and distal extremities with relative sparing of the trunk);
2. the first lesions of the rash appeared on the oral mucosa or palate, or on the face or forearms;
3. the patient appears toxic or moribund;
4. lesions progressed slowly (*i.e.*, the individual lesions evolved from macules to papules to pustules; each stage lasts 1-2 days);
5. lesions on the palms or soles.

A person is considered as **high risk** for smallpox if he or she meets all three major criteria. Immediate action should be taken to make sure that contact precautions and respiratory isolation are in place. These patients should be reported to local and/or state health authorities immediately. Obtain digital photographs if possible and consult with dermatology and/or infectious disease experts. Following such consultation, if the patient is still considered to be high risk, the state health department will immediately report the case to CDC and arrangements will be made for laboratory testing for smallpox virus.

A person considered at **moderate risk** of smallpox must have a febrile prodrome and either one other major criterion or ≥4 minor. These patients should be isolated and be evaluated urgently to determine the cause of the illness. Persons classified as high or moderate risk be seen in consultation with a specialist in infectious diseases and/or dermatology whenever possible. Any person who did not have a febrile prodrome is considered **low risk**, as are persons who had a febrile prodrome and less than 4 minor criteria. These patients should be managed as clinically indicated.

A case investigation worksheet and a poster that includes the rash illness algorithm, and information on differential diagnosis is available from the CDC smallpox website at http://www.cdc.gov/smallpox.

LABORATORY AND PATHOLOGY DIAGNOSIS

If a case is classified as high risk after evaluation using the algorithm, it fits the clinical case definition for smallpox and therefore should be considered a probable smallpox case until smallpox virus laboratory results are completed. For such a case, do not perform other lab testing for other diagnoses.

For a patient who meets the criteria for moderate risk, **the most important laboratory procedure is rapid diagnostic testing for varicella zoster virus (VZV)**. Laboratory testing should be done in consultation with an infectious disease or dermatology specialist. Smallpox virus testing is not indicated for cases that do not meet the clinical case definition. In the absence of smallpox (disease prevalence of zero), the predictive value of a positive lab test is extremely low (close to zero). Limiting requests for smallpox testing to cases that fit the clinical case definition will minimize the

risks of a false positive lab result which would have extremely serious consequences.

Since varicella was the most common disease confused with smallpox in the past and the most common diagnoses in smallpox false alarms in the immediate posteradication era, rapid VZV diagnostic tests are important for evaluation of suspected smallpox cases. There are a variety of rapid methods for detecting VZV in clinical material. The most useful is direct fluorescent antibody, or DFA. This method detects VZV directly in cells using anti-VZV antibody conjugated to fluorescein dye. DFA is very sensitive and specific but is critically dependent on careful collection of material from a lesion. Detection of VZV DNA by polymerase chain reaction testing of vesicular fluid or scabs can also be used for rapid detection of VZV in clinical material. Real time PCR assays take 4-6 hours to perform. Virus particles consistent with VZV can be detected using electron microscopy. Rapid diagnostic testing for VZV is generally available in at least one facility (private labs, academic hospital centers) in all large cities, in some local and in all state health department facilities. Other testing should be done as clinically indicated and may include testing for herpes simplex viruses, enteroviruses and syphilis among many possible tests.

Tzanck smear, although not diagnostic of VZV infection, is a rapid and easily performed test in hospitals with a pathology laboratory and is frequently available at the local level. A positive Tzanck smear confirms an alphaherpesvirus infection (either VZV or HSV).

Skin biopsies, if clinically indicated, can assist with diagnoses on the basis of histopathology or can be confirmatory if immunohistochemistry tests are available.

Currently, laboratory procedures for isolation of variola virus in clinical specimens should be done only by the Centers for Disease Control and Prevention in Atlanta. If the patient's clinical characteristics indicate a high risk for smallpox, the state health department should be contacted immediately. The diagnosis of an Orthopoxvirus infection can be made rapidly by electron microscopic examination of pustular fluid or scabs. Orthopox generic PCR tests are available but do not distinguish between vaccinia, variola and other poxvirus infections. Differentiation of Orthopoxviruses is made by nucleic acid-based testing, such as PCR. Serologic tests have also been developed to assist in the diagnosis of acute orthopoxvirus infection and direct antigen detection tests for variola virus are under development.

MEDICAL MANAGEMENT

A suspected case of smallpox is a public health and medical emergency. Any person whose clinical characteristics meet the clinical case definition for smallpox (see below) must be isolated and reported immediately to the local and/or state health department.

Strict respiratory and contact isolation of confirmed or suspected smallpox patients is critical to limit the exposure to the virus. Smallpox patients are infectious until all crusts have separated. Although droplet spread is the major mode of person to person smallpox transmission, airborne transmission through fine particle aerosol can rarely occur. Therefore, airborne precautions using a negative air pressure room with high efficiency particulate air filtration should be initiated immediately for hospitalized high risk or confirmed smallpox patients. This is the same isolation precaution that is taken for other infectious diseases with respiratory transmission, such as varicella.

Smallpox Medical Management

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

All personnel who have contact with a suspected or confirmed case of smallpox should utilize appropriate protective equipment. This includes using properly fitted respirators (masks) of N95 quality or higher. In addition, personnel should use disposable gloves, gowns and shoe covers for all contact with patients. This precaution is to prevent inadvertent transmission of variola virus from clothing or other contaminated items to susceptible persons. Personnel should remove and correctly dispose of all protective clothing before contact with other people. Reuseable bedding and clothing can be autoclaved or laundered in hot water with bleach to inactivate the virus. People who come into contact with materials potentially contaminated with smallpox virus, such as laundry handlers, housekeeping, and laboratory personnel should utilize appropriate protective equipment. If a case of smallpox is confirmed, these personnel should be vaccinated before handling contaminated materials.

Medical management of a person with smallpox is primarily supportive. No antiviral drug is currently approved by the Food and Drug Administration for the treatment of smallpox. Recent studies suggest that the antiviral drug cidofovir might be useful as a therapeutic agent. However, the drug must be administered intravenously, and can cause serious renal toxicity. Cidofovir administered for the treatment of smallpox would be an off-label use. Antiviral therapy with cidofovir or other drugs subsequently found to have antivariola activity might be considered but would be used under an investigational new drug protocol and by an infectious diseases specialist.

EPIDEMIOLOGY

RESERVOIR

Smallpox Epidemiology

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

Although animals can be experimentally infected with variola, humans are the only natural host. There is no chronic carrier state, and no known animal reservoir. Since the early 1980s (*i.e.*, following global smallpox eradication) the only known locations of variola virus are at the CDC in Atlanta, and at the State Research Center of Virology and Biotechnology in Koltsovo, Russia.

TRANSMISSION

Transmission of smallpox occurs through inhalation of airborne variola virus, usually droplets expressed from the oral, nasal, or pharyngeal mucosa of an infected person. Most transmission results from direct fact-to-face contact with an infected person, usually within a distance of 6 feet, or from physical contact with a person with smallpox or contaminated articles. Although variola virus could remain viable for years in dried crusts of skin lesions, transmission from crusts is uncommon, probably because virus is enmeshed in a fibrin matrix.

COMMUNICABILITY

A person infected with variola virus is not infectious during the incubation period, or the first day or two of the prodromal stage of the illness. The patient becomes infectious with the first appearance of the rash, which was often accompanied by lesions in the mouth and pharynx. The patient becomes infectious and can transmit the virus throughout the course of the illness (*i.e.*, until all crusts separated). Transmission is most frequent during the first week of the rash, while most skin lesions are intact (*i.e.*, vesicular or pustular). Virus is present in material draining from ruptured pustules and in crusts for a longer period, but infection from this source appears to be less frequent. In general persons with a severe rash and involvement of the mouth and pharynx, and those with a cough are more infectious than those with a slight rash. Household secondary attack rates are generally 50%-60%.

Smallpox Epidemiology

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

Natural transmission of smallpox in a population is relatively slow. There is an interval of two to three weeks between each generation of cases. Smallpox generally spreads less widely and less rapidly than varicella or measles, probably because transmission of variola virus doesn't occur until the onset of rash and generally requires close face to face contact for spread. At the time of rash onset, most patients are already confined to bed because of the high fever and toxemia of the prodromal stage of the illness. However, people with severe prodromal illness may seek medical attention. Consequently, hospitals are a frequent source of infection because of transmission from unrecognized hospitalized cases.

Secondary cases of smallpox are usually limited to those who come in contact with the infected person in the household or hospital. During the global eradication program, it was possible to interrupt the chain of transmission of smallpox by isolating smallpox patients in a setting in which they had contact only with adequately vaccinated or previously infected people. This limited the next potential generation of cases to the household and close contacts of the index case or cases. Contacts were identified and immediately vaccinated. Contacts who became ill were also isolated to establish a barrier to further transmission. This strategy was found to be effective even if community vaccination levels were low.

TEMPORAL PATTERN

In temperate areas, the seasonality of smallpox was similar to that of measles and varicella, with incidence highest during the winter and spring. In tropical areas, seasonal variation was decreased and the disease was present throughout the year.

SECULAR TRENDS

The last case of smallpox in the United States was reported in 1949. In the early 1950s, an estimated 50 million cases of smallpox occurring worldwide each year. Ten to 15 million cases occurred in 1966, when the disease had already been eliminated in 80 percent of the world.

SMALLPOX ERADICATION

Smallpox Eradication

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

The intensified global smallpox eradication program began in 1966. The initial campaign was based on a two-fold strategy. First, mass vaccination campaigns in each country, using vaccine of ensured potency and stability, that would reach at least 80% of the population. Second, the development of surveillance systems to detect and contain cases and outbreaks.

The program had to surmount numerous problems, including lack of organization in national health services, epidemic smallpox among refugees fleeing areas stricken by civil war and famine, shortages of funds and vaccine, and a host of other problems posed by difficult terrain, climate, and cultural beliefs. In addition, it was soon learned that even when 80% of the population was vaccinated, smallpox often persisted. Soon after the program began it became apparent that by isolating people with smallpox and vaccinating their contacts, outbreaks could be more rapidly contained, even in areas where vaccination coverage was low. This strategy was called **surveillance and containment**, and it became the key element in the global eradication program.

Although setbacks occurred, the surveillance and containment strategy was an enormous success. Using it, the last case of smallpox in Brazil was reported in 1971, and Indonesia's last case occurred in 1972. India, Pakistan and Bangladesh, with a population at that time of more than 700 million, was a particular challenge. But with intensive house to house searches and strict containment, the last case of variola major- the most deadly type of smallpox- occurred in Bangladesh in October 1975.

By the end of 1975, smallpox persisted only in the Horn of Africa. Conditions were very difficult in Ethiopia and Somalia, where there were few roads. Civil war, famine, and refugees made the task even more difficult. An intensive surveillance and containment and vaccination program was undertaken in the spring and summer of 1977. As a result, the world's last indigenous patient

with smallpox was a hospital cook in Merka, Somalia, on October 26, 1977. Searches for additional cases continued in Africa for more than 2 years, during which time thousands of rash illnesses were investigated. None proved to be smallpox.

The last cases of smallpox on earth occurred in an outbreak of 2 cases (one of which was fatal) in Birmingham, England in 1978. This outbreak occurred because variola virus was carried by the ventilation system from a research laboratory to an office one floor above the laboratory. In 1980 the World Health Assembly certified the global eradication of smallpox and recommended that all countries cease vaccination. The World Health Organization also recommended that all laboratories either destroy their remaining stocks of variola virus or transfer them to one of two WHO reference laboratories - the Institute of Viral Preparations in Moscow, or the Centers for Disease Control and Prevention in Atlanta. All laboratories were believed to have complied with this request.

CASE DEFINITION

A clinical case of smallpox is defined as an illness with acute onset of fever $\geq 101^{o}$F followed by a rash characterized by firm, deep-seated vesicles or pustules in the same stage of development without other apparent cause.

This case definition will not detect an atypical presentation of smallpox including hemorrhagic or flat-type disease. In addition, given the extremely low likelihood of smallpox occurring, a case definition has been developed that provides a high level of specificity (*i.e.*, vesicular rash illness), rather than a high level of sensitivity (*i.e.*, maculopapular rash illness). In the event of a smallpox outbreak, the case definition would be modified to increase sensitivity.

SMALLPOX (VACCINIA) VACCINE

The first attempts to prevent smallpox were in China and India in the 9th century, and involved either nasal insufflation of powdered smallpox scabs, or scratching material from a smallpox lesion into the skin. This procedure was know as variolation, and if successful, produced lasting immunity to smallpox. However, because the person was infected with variola virus, a severe infection could result, and the person could transmit smallpox to others.

In 1796 **Edward Jenner**, a doctor in rural England, discovered that immunity to smallpox could be produced by inoculating a person with material from a cowpox lesion. Cowpox is a poxvirus in the same family as variola. Jenner called the material used for inoculation vaccine, from the root word *vacca*, which is Latin for cow. The procedure was much safer than variolation, and did not involve a risk of smallpox transmission. Vaccination to prevent smallpox was soon practiced all over the world.

Smallpox Vaccine

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

At some time during the 19th century, the cowpox virus used for smallpox vaccination was replaced by vaccinia virus. Vaccinia is in the same family as cowpox and variola, but is genetically distinct from both. The origin of vaccinia virus, and how it came to be in the vaccine is not known.

CHARACTERISTICS

Smallpox Vaccine

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

The smallpox vaccine currently available in the United States (Dryvax, produced by Wyeth) is a **live virus preparation of infectious vaccinia virus**. Smallpox vaccine does not contain smallpox (variola) virus. The current vaccine was prepared in the early 1980s from calf lymph with a seed virus derived from the NYCBOH strain of vaccinia virus. The vaccine is provided as a lyophylized (freeze-dried) powder in a 100 dose vial, and contains the antibiotics polymyxin B, streptomycin, tetracycline and neomycin. The diluent used to reconstitute the vaccine is 50% glycerin, and contains a small amount of phenol as a preservative.

Approximately 15 million doses of vaccine are available now in the United States. Testing has shown that existing supplies of vaccine could be diluted by a 1 to 5 ratio and still remain as effective and safe as full-strength vaccine. An additional 200 million additional doses of vaccine are being produced using cell culture methods to be available in case of an introduction of smallpox. These new vaccines do not contain antibiotics. They will be distributed as freeze-dried powder and will be reconstituted using a diluent to that used for calf lymph vaccine.

The vaccine is administered by using a multiple puncture technique with a special bifurcated needle. Detailed information concerning reconstitution and administration of smallpox vaccine are available on the CDC smallpox website at http://www.cdc.gov/smallpox.

Response to Smallpox Vaccination

- Neutralizing antibody develops
  - 10 days after primary vaccination
  - 7 days after revaccination
- >95% of primary vaccinees develop detectable neutralizing antibody
- Antibody persists >10 years

IMMUNOGENICITY AND VACCINE EFFICACY

Neutralizing antibodies induced by vaccinia vaccine are genus-specific and cross-protective for other Orthopoxviruses (*e.g.*, monkeypox, cowpox, and variola viruses). Neutralizing antibodies are detectable 10 days after primary vaccination, and 7 days after revaccination. Although the level of antibody that protects against smallpox infection is unknown, after percutaneous administration of a standard dose of vaccinia vaccine, >95% of primary vaccinees (*i.e.*, persons receiving their first dose of vaccine) will develop neutralizing or hemagglutination inhibition antibody at a titer of >1:10. Neutralizing antibody titers of >1:10 persist among 75% of persons for 10 years after receiving second doses and up to 30 years after receiving three doses of vaccine.

Smallpox Vaccine Efficacy

- Clinical efficacy estimated in household contact studies
- 91%-97% reduction in cases among contacts with vaccination scar
- Studies did not consider time since vaccination or potency of vaccine

The efficacy of smallpox vaccine has never been measured precisely in controlled trials. However, protection has been determined in studies of people exposed to a smallpox patient in their household. These studies indicated a 91%-97% reduction in smallpox among

contacts with a vaccination scar compared to contacts without a scar. However, these studies did not always consider the time since vaccination or potency of vaccine, so may underestimate protection.

Epidemiologic studies demonstrated that a high level of protection (nearly 100%) against smallpox persists for up to 5 years after primary vaccination and substantial but waning immunity for ten years or more. Antibody levels after revaccination can remain high longer, conferring a greater period of immunity than occurs after primary vaccination alone. Although smallpox vaccination in the remote past may not completely protect against smallpox, vaccinated people appear to have less severe disease. Studies of smallpox cases imported into Europe in the 1950s and 1960s demonstrated fewer fatalities among vaccinated people compared to those who were unvaccinated. The fatality rate among people vaccinated <10 years before exposure was 1.3%, 7% among those vaccinated 11 to 20 years prior, and 11% among those vaccinated 20 or more years prior to infection. In contrast, 52% of unvaccinated people died.

Smallpox vaccination also provides protection if administered after an exposure to smallpox. **Postexposure efficacy** has been estimated in household contact studies in Pakistan and India. These studies indicate that secondary cases in households were reduced up to 91% compared with unvaccinated people. The lowest secondary attack rates occurred in persons vaccinated <7 days after exposure. In these studies, smallpox was generally less severe (*i.e.*, modified type) in persons who received postexposure vaccination.

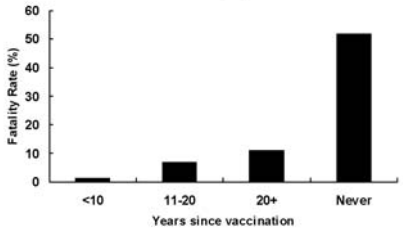
Following vaccination, vaccinia virus replicates in the basal cells of the epidermis, resulting in the development of a lesion at the site of vaccination. A papule develops at the inoculation site 3-4 days after primary vaccination. Approximately 7 days following primary vaccination, a vesicle (a blister containing clear fluid) surrounded by erythema (a "Jennerian vesicle") forms at the site. The vesicle becomes pustular by 7 to 11 days after vaccination. Maximum erythema occurs 8 to 12 after vaccination. The erythema then subsides, the pustule dries, and a crust develops 2 to 3 weeks after vaccination. In the third week, the crust separates, leaving a permanent scar at the vaccination site. This response to vaccination is called a **major reaction**, and indicates that virus replication has taken place and vaccination was successful. **A person is considered protected with the development of a major reaction at the vaccination site**. A revaccinated person often develops a skin reaction similar to that after primary vaccination, but the lesion progresses faster than after primary vaccination.

Some persons do not develop a typical skin lesion after vaccination. All responses other than major reactions are referred to as **equivocal**. There are several possible causes of equivocal reactions. The person may be sufficiently immune to suppress viral replication. The person may be allergic to a component of the vaccine which leads to a hypersensitivity reaction at the site. An equivocal reaction could also be caused by insufficiently potent

Duration of Immunity Following Smallpox Vaccination

- High level of protection (~100%) for up to 5 years following vaccination
- Substantial but waning immunity for ≥10 years
- Reduction in disease severity among previously vaccinated persons

Smallpox Fatality Rate by Time Since Vaccination - Europe, 1950-1971*



*Mack TM. J Infect Dis 1972;125:161-9.

Postexposure Vaccine Efficacy

- Secondary attack rates reduced up to 91% compared to unvaccinated contacts
- Lowest disease rates among persons vaccinated <7 days after exposure
- Disease generally less severe (modified-type) in persons receiving postexposure vaccination

Clinical Response to Smallpox Vaccination*

Symptom/sign	Time after Vac
Papule	3-4 days
Vesicle	5-6 days
Pustule	7-11 days
Maximum erythema	8-12 days
Scab	14 days
Scab separation	21 days

*typical response in a nonimmune person

Clinical Response to Smallpox Vaccination

- Major (primary) reaction
  - Indicates viral replication has occurred and vaccination was successful
  - Considered to be protected with the development of a major reaction
- Equivocal reaction
  - Indicates immune suppression of viral replication, allergic reaction without production of immunity, incorrect vaccination technique, or impotent vaccine
  - Revaccinate immediately

Evolution of U.S. Smallpox Vaccine Recommendations

- 1972 Discontinue routine vaccination
- 1976 Discontinue vaccination of HCWs
- 1980 Vaccine recommended for lab workers
- 1990 Discontinue vaccination of military
- 1991 Consider vaccine for HCWs exposed to recombinant vaccinia
- 2001 Bioterrorism guidelines
- 2002 Smallpox Response Teams

Smallpox Vaccine Indications in Nonemergency Situations

- Laboratory workers who handle cultures or animals infected with nonhighly attenuated vaccinia
- Laboratory workers exposed to other Orthopoxviruses that infect humans
- Consider for other health care workers with contact with contaminated material
- Public health, hospital, and other personnel who may need to respond to a smallpox case or outbreak
- Persons who vaccinate others

Smallpox Vaccine Indications in Emergency Situations*

- Persons exposed to initial release
- Close contact with confirmed or suspected case
- Direct care or transportation of confirmed or suspected case
- Laboratory personnel
- Persons with risk of contact with infectious materials from case
- Other groups as recommended by public health authorities

*following confirmation of a case of smallpox

vaccine or incorrect administration technique. In general, a person who has an equivocal response to vaccination should be revaccinated using vaccine from another vial if possible. More information on interpretation of response to vaccination is available in the smallpox vaccine ACIP statement.

Live vaccinia virus is present at the vaccination site beginning 3 to 4 days after vaccination, and until the crust separates from the skin. Since the developing vaccinia lesion usually itches, care must be taken to avoid scratching, then touching other parts of the body, such as the eye, or other people. This could transfer the vaccine virus to these sites or individuals. Washing hands immediately after touching the vaccination site or dressing is very important in preventing this.

VACCINATION SCHEDULE AND USE

Routine childhood smallpox vaccination was discontinued in the United States in 1972. Routine vaccination of healthcare workers was discontinued in 1976, and among military recruits in 1990. In 1980 smallpox vaccine was recommended for laboratory workers who were at occupational risk for exposure to vaccinia or other orthopoxviruses. In 1991 the Advisory Committee on Immunization Practices recommended that other healthcare workers who could be exposed to vaccinia or recombinant vaccinia be considered for vaccination. Guidelines for use of smallpox vaccine in the event of an intentional release of smallpox virus were first published in 2001.

For routine nonemergency use (i.e., in the absence of smallpox disease) **vaccination is recommended for laboratory workers who directly handle cultures or animals contaminated or infected with nonhighly attenuated vaccinia viruses** (*e.g.*, the NYCBOH, Temple of Heaven, Copenhagen, or Lister vaccinia strains), and recombinant vaccinia viruses derived from nonhighly attenuated vaccinia strains. Vaccination is also recommended for laboratory workers exposed to other orthopoxviruses that infect humans (*e.g.*, monkeypox or cowpox). Vaccination can be considered for other healthcare workers who come into contact with materials such as dressings that may be contaminated with vaccinia or recombinant vaccinia. This could occur, for example, in the course of a clinical trial in which humans were administered vaccines containing recombinant vaccinia viruses. **Vaccination is also recommended for public health, hospital, and other personnel who may need to respond to a smallpox case or outbreak, and for persons who administer the vaccine to others.**

In the event of an intentional release of variola virus, vaccination would be recommended for those exposed to the initial release, contacts of people with smallpox, and others at risk of exposure. Persons at risk of exposure would include those involved in the direct medical or public health evaluation, care or transportation of confirmed or suspected smallpox patients; labora-

tory personnel who collect or process clinical specimens from confirmed or suspected smallpox patients; people who may have contact with infectious materials, such as those responsible for medical waste disposal, linen disposal or disinfection, and room disinfection in a facility where smallpox patients are present; and other groups (*e.g.,* medical, law enforcement, emergency response, or military personnel) as recommended by public health authorities.

The **schedule** for smallpox vaccine is 1 successful dose (*i.e.*, a dose that results in a major reaction at the vaccination site). In routine circumstances the vaccine should not be administered to persons <18 years of age. In an emergency (postrelease) situation, there would be no age limit for vaccination of persons exposed to a person with confirmed smallpox.

Persons with occupational exposure to nonhighly attenuated vaccinia viruses, recombinant viruses derived from nonhighly attenuated vaccinia viruses, or other nonvariola orthopoxviruses should be revaccinated at least every 10 years. To ensure an increased level of protection against more virulent nonvariola orthopoxviruses (*e.g.*, monkeypox), empiric revaccination every 3 years can be considered.

ADVERSE REACTIONS FOLLOWING VACCINATION

A vesicular or pustular skin lesion at the site of inoculation indicates a successful vaccination, or "take". In several recent studies of old and new vaccines given to unvaccinated adults, the average size of the pustule at 2 weeks after vaccination was 12 millimeters. The average size of erythema surrounding the pustule was 16 to 24 millimeters, and average induration was 11 to 15 millimeters.

Some vaccinees may have larger amounts of erythema and induration that can be mistaken for cellulitis. These reactions generally improve within 24 to 48 hours without specific therapy but may require clinical evaluation to rule out bacterial cellulitis.

Forty to 47 percent of the vaccinees reported mild pain at the site of inoculation. But 2%-3% reported the pain as severe. Axillary lymphadenopathy was reported in about one third of recipients. Most lymphadenopathy was mild, but in 3%-7% it was considered moderate, *i.e.*, bothersome to the vaccinee but not otherwise interfering with normal activities.

Fever is common after administration of smallpox vaccine. In a recent study of Dryvax given to unvaccinated adults, 5%-9% reported a fever of $\geq 100^{o}$F, and 3% reported temperature of $\geq 102^{o}$ F. Fever is most common 7 to 12 days after vaccination. In addition to fever, adult vaccinees also report a variety of constitutional symptoms, including headache, myalgias, chills, nausea, and fatigue on or about the eighth or ninth day after vaccination. One or 2 percent of recipients reported these symptoms as severe.

Historically, fever was more common among children. In past stud-

Smallpox Vaccine

- Schedule
  - 1 successful dose
- Revaccination
  - 10 years (nonhighly attenuated vaccinia and recombinants)
  - 3 years (more virulent Orthopoxviruses)

Smallpox Vaccine Local Reactions Among Susceptible Adults

- Pain, swelling, erythema at vaccination site
- Regional lymphadenopathy
  - Begins 3-10 days after vaccination
  - Can persist for 2-4 weeks after vaccination site heals

Smallpox Vaccine Reactions Among Susceptible Adults

- Elevated temperature
  - 17% $\geq 100^{o}$ F
  - 1.4% $\geq 102^{o}$ F
- Systemic symptoms (malaise, myalgias)
- 36% sufficiently ill to miss work, school, or recreational activities or had trouble sleeping

Smallpox Vaccine Adverse Reaction Rates*

Reaction	Primary Vaccination
Inadvertent inoculation	25-529
Generalized vaccinia	23-242
Eczema vaccinatum	10-39
Progressive vaccinia	0.9-1.5
Postvaccinial encephalitis	3-12
Death	1

*Rates per million primary vaccinations

ies, about 70% of children experience 1 or more days of temperature of ≥100°F after primary vaccination. Fifteen to 20 percent of children experienced temperatures ≥102°F.

Inadvertent Inoculation

- Caused by transfer of vaccinia virus from site of vaccination to other areas of the body
- Most commonly on face, eyelid, nose, mouth, rectum, genitalia
- Most lesions heal spontaneously without specific treatment

Vaccinia virus is present at the site of vaccination beginning about 4 days after vaccination. Maximum viral shedding from the vaccination site occurs 4-14 days after vaccination, but vaccinia can be recovered from the site until the crust separates from the skin. **Inadvertent inoculation** (*i.e.*, transfer of vaccinia from the vaccination site to another part of the body) is the most frequent complication of smallpox vaccination and accounts for approximately half of all complications of primary vaccination and revaccination. Studies in 1968 estimated the rate of inadvertent inoculation to be 529 cases per million primary vaccinations. The most common sites involved are the face, eyelid, nose, mouth, genitalia, and rectum. Most lesions heal without specific treatment. Involvement of the eye may result in scaring of the cornea and significant impairment of vision.

A variety of **erythematous or urticarial rashes** can occur approximately 10 days after primary vaccination. The vaccinee is usually afebrile with this reaction, and the rash resolves spontaneously within 2-4 days. Rarely, bullous erythema multiforme (Stevens Johnson syndrome) occurs.

Generalized Vaccinia

- Results from viremia with implantations in the skin
- Occurs in the absence of eczema or other pre-existing skin diseases
- Vesicles or pustules on normal skin distant from vaccination site
- Usually minor illness with little residual damage

Generalized vaccinia is another type of rash following smallpox vaccination. This condition is believed to result from a vaccinia viremia with implantations in the skin in persons without eczema or other pre-existing skin disease. It consists of vesicles or pustules appearing on normal skin distant from the vaccination site. Most rashes labeled as generalized vaccinia produce only minor illness with little residual damage. The rash is generally self limited and requires minor or no therapy except among patients whose conditions might be toxic, or who have serious underlying immunosuppressive illnesses. In the 1968 studies, rashes diagnosed as generalized vaccinia occurs at a rate of 242 per million primary vaccinations.

Moderate and severe complications of vaccinia vaccination include eczema vaccinatum, progressive vaccinia, and postvaccinial encephalitis. These complications are rare but occur >10 times more often among primary vaccinees than among revaccinees and are more frequent among infants than among older children and adults. It is estimated that 14-52 persons per million primary vaccinations will experience potentially life-threatening adverse reactions.

Myopericarditis is the inflammation of heart muscle and/or the membrane that surrounds the heart. There were reports of this condition following smallpox vaccination in the 1950s and 1960s, but these cases were associated with vaccine strains not currently used. Myopericarditis was not an anticipated adverse reaction to the smallpox vaccine when the National Smallpox Vaccination Program began in December 2002. However, cardiac symptoms

related to myocarditis were reported in the civilian smallpox vaccination program on March 28, 2003, and by July 25, 2003 18 cases had been reported in the military vaccination program. These cases occurred at a frequency of 1 case in 12,819 primary vaccinations.

Eczema vaccinatum is a localized or systemic dissemination of vaccinia virus in persons who have eczema or atopic dermatitis, or a history of eczema or atopic dermatitis, or among contacts of vaccinees with eczema or atopic dermatitis, or a history of these skin conditions. **Eczema vaccinatum can occur regardless of whether the skin disease is active or quiescent.** Usually the illness is mild and self limited but can be severe or fatal. The most serious cases among vaccine recipients occur among primary vaccinees. Severe cases have been observed after contact of recently vaccinated persons with persons who have active eczema or atopic dermatitis, or a history of these skin conditions. In the 1968 studies, eczema vaccinatum was estimated to occur in 10-39 persons per million primary vaccinations.

Eczema Vaccinatum

- Generalized spread of vaccinia on skin of patients with eczema or atopic dermatitis, or past history of eczema or atopic dermatitis
- Occurs in vaccinees and contacts
- Can occur whether eczema is active or quiescent
- May be severe or fatal

Progressive vaccinia, also known as vaccinia necrosum, is a severe illness characterized by progressive necrosis in the area of vaccination, often with metastatic lesions. It occurs almost exclusively among persons with cellular immunodeficiency, but can occur in persons with humoral immunodeficiency. In the 1968 studies, it occurred in approximately 1-2 persons per million primary vaccinations. Progressive vaccinia was almost always fatal before the introduction of vaccinia immune globulin and antiviral agents. Progressive vaccinia may be more common now, with HIV and post-transplant immunosuppression widely prevalent. Therapy includes aggressive treatment with vaccinia immune globulin and possibly antiviral drugs.

Progressive Vaccinia

- Progressive necrosis at site of vaccination, often with metastatic lesions
- Occurs in patients with impaired immunologic function, particularly cellular immunodeficiency
- Frequently fatal

Postvaccinial encephalitis has been reported in 3-12 persons per million primary vaccinations. In the majority of cases, post-vaccinal encephalitis affects primary vaccinees <12 months of age or adolescents and adults receiving a primary vaccination. It presents with any of a variety of central nervous system signs, such as ataxia, confusion, paralysis, seizures, or coma. Most cases are believed to result from autoimmune or allergic reactions rather than direct viral invasion of the nervous system. Approximately 15%-25% percent of affected vaccinees with this complication die, and 25% develop permanent neurological sequelae. There is no specific therapy for postvaccinial encephalitis.

Postvaccinal Encephalitis

- Highest risk among children <12 months of age and older persons receiving primary vaccination
- Believed to result from autoimmune or allergic reaction
- Frequently fatal or neurologic sequelae

Fetal vaccinia is a rare complication of smallpox vaccination. Fewer than 50 cases of fetal vaccinia infection have been reported, usually after primary vaccination of the mother in early pregnancy. Fetal vaccinia usually results in stillbirth or death of the infant soon after delivery. Smallpox vaccine is not known to cause congenital malformations.

Fetal Vaccinia

- <50 fetal vaccinia cases reported in world literature
- Most result from primary vaccination of mother early in pregnancy
- Usually results in stillbirth or death of infant soon after delivery
- Congenital malformations not reported

Death resulting from smallpox vaccination is rare, with approximately 1 death per million primary vaccinations and 1 death per 4

million revaccinations. Death is most often the result of postvaccinial encephalitis or progressive vaccinia.

Guidelines for the evaluation and management of adverse reactions following smallpox vaccine were published in 2003 in *Morbidity and Mortality Weekly Report (MMWR)*. These guidelines are available on the CDC smallpox website at http://www.cdc.gov/smallpox.

CONTRAINDICATIONS AND PRECAUTIONS TO VACCINATION

As with all vaccines, smallpox vaccine is contraindicated for persons who have experienced a serious allergic reaction to a prior dose of vaccine, or to a vaccine component. Calf lymph vaccine (Dryvax) contains trace amounts of polymyxin B, streptomycin, tetracycline, and neomycin. The diluent contains glycerin and phenol. The vaccine does not contain sulfa-type antibiotics or penicillin. The new cell-culture vaccines do not contain antibiotics.

People with significant **immunosuppression**, or who have an **immunosuppressed household contact** should not receive smallpox vaccine in a non-emergency situation. Replication of vaccinia virus can be enhanced among people with immunodeficiency diseases and immunosuppression. Significant immunosuppression can be caused by many diseases, including leukemia, lymphoma, generalized malignancy; solid organ or stem cell transplantation; and cellular or humoral immunity disorders, including HIV infection. Some autoimmune conditions and/or drugs used to treat autoimmune conditions may cause significant immunosuppression. Therapies that can cause immunosuppression include alkylating agents, antimetabolites, radiation, or high dose corticosteroid therapy. Many experts suggest that prednisone doses of 2 milligrams per kilogram of body weight per day or higher or 20 milligrams per day or higher for 14 days or more be considered immunosuppressive for the purpose of live virus vaccination. As with other live vaccines, those on high levels of these drugs should not be immunized for three months after their last dose.

Smallpox Vaccine
Contraindications and Precautions
(Nonemergency Situations)

- Serious allergic reaction to a vaccine component or following prior dose
- Immunosuppression in the recipient or household contact
- Pregnancy in the recipient or household contact
- Breastfeeding

People with physician-diagnosed **heart disease** should not receive the smallpox vaccine. This recommendation is based on findings of cardiac symptoms such as chest pain, palpitations and shortness of breath that were first detected in late March of 2003, and is further supported by the recognition of myopericarditis as an adverse reaction. In addition to physician-diagnosed heart disease, individuals with three of the five heart disease **risk factors** (hypertension, hyperlipidemia, current smoker, diabetes or a first degree relative with a heart condition before the age of fifty) are contraindicated from receiving the smallpox vaccine.

Smallpox Vaccine
Contraindications and Precautions
(Nonemergency Situations)

- Eczema or atopic dermatitis (current or past history) in the recipient or household contact
- Acute, chronic, or exfoliative skin conditions (until improved or resolved) in the recipient or household contact
- Children <12 months of age
- Moderate or severe acute illness

Live viral vaccines are contraindicated during **pregnancy**. Smallpox vaccine should not be administered to pregnant women or persons with a pregnant household contact for nonemergency indications. Pregnancy should also be avoided for at least 4 weeks after vaccination. Women who are breastfeeding should not be vac-

cinated because the close contact that occurs during this activity could increase the chance of transmission of the vaccine virus to the breastfeeding infant.

Because of the increased risk for eczema vaccinatum, smallpox vaccine should not be administered to persons with **eczema or atopic dermatitis, or a past history of these conditions**. Persons who have a household contact with eczema or atopic dermatitis or a history of these conditions should also not be vaccinated.

People with other types of **acute, chronic, or exfoliative skin conditions** (e.g., burns, varicella, herpes zoster, impetigo, severe acne, or psoriasis) may be at increased risk of inadvertent inoculation. People with exfoliative skin conditions should not be vaccinated until the condition is controlled or resolves. In addition, persons with household contacts with acute, chronic, or exfoliative skin conditions should not be vaccinated until the skin condition in the household contact is controlled or resolves.

Children <12 months of age should not be vaccinated. All vaccinated people should take precautions to prevent virus transmission to young children and other household contacts. Since smallpox vaccine is currently recommended only for persons with occupational risk of exposure to vaccinia or recombinant vaccinia viruses, and for healthcare and public health response team members, vaccination is not indicated for infants or children <18 years of age.

As with all vaccines, vaccination should be deferred for people with **moderate or severe acute illnesses**.

In the event of an exposure to smallpox, there would be no contraindications to vaccination. In this situation, the benefit of vaccination would outweigh the risk of a complication from the vaccine. In a postrelease situation, contraindications and precautions for use of smallpox vaccine in a person who has not been exposed to smallpox would be the same as those in a nonemergency situation.

Smallpox Vaccine
Contraindications and Precautions
Emergency (postrelease) Situations

- Exposed persons – no contraindications
- Unexposed persons – same as nonemergency situations

VACCINIA IMMUNE GLOBULIN (VIG)

The only product currently available for treatment of complications of vaccinia vaccination is VIG, which is a sterile solution of the immunoglobulin fraction of plasma from persons vaccinated with vaccinia vaccine. VIG is effective in the treatment of eczema vaccinatum, serious generalized vaccinia, and serious manifestations of inadvertent inoculation such as ocular vaccinia. VIG is also indicated for progressive vaccinia and has variable effectiveness in treating this complication. Since postvaccinial encephalitis is not due to virus multiplication, VIG is not effective in treating this adverse reaction. VIG has no role in the treatment of smallpox.

Vaccinia Immune Globulin

- Immunoglobulin fraction of plasma from persons vaccinated with vaccinia vaccine
- Effective for treatment of eczema vaccinatum, progressive vaccinia, severe generalized vaccinia, and ocular vaccinia
- Not effective in postvaccinial encephalitis

Current supplies of VIG are limited, and must be used under an Investigational New Drug (IND) protocol. VIG should be reserved for treatment of vaccine complications with serious clinical mani-

festations. The recommended dosage of the currently available VIG for treatment of complications is 0.6 ml/kg of body weight. VIG must be administered intramuscularly and should be administered as early as possible after the onset of symptoms. CDC is currently the only source of VIG for civilians. A new intravenous formulation of VIG is being produced and will be available for treatment of adverse events.

Cidofovir is an antiviral medication that is currently licensed for the treatment of CMV retinitis. In vitro and animal studies with this drug have shown some activity against vaccinia virus, but it is unclear how well it would work in treating vaccinia infections in humans. Because it is not licensed for this indication, use of cidofovir for treating vaccinia infections should be done under an investigational new drug protocol with careful monitoring. Cidofovir is a second line treatment for complications of smallpox vaccination as VIG is still considered the standard treatment. CDC is developing the investigative protocol for use of this drug.

VACCINE STORAGE AND HANDLING

Vaccine Storage and Handling

- Stable indefinitely at –20°C
- Store unreconstituted vaccine at 2°-8° C
- Reconstituted vaccine must be used within 90 days
- Avoid contamination after opening vial

Lyophylized smallpox vaccine is stable indefinitely at temperatures of -20°C or less. Unreconstituted vaccine should be stored at refrigerator temperature (2-8°C). The vaccine should be used within 90 days of reconstitution. Because the vaccine vial must be opened in order to prepare a dose for administration (i.e., the bifurcated needle is dipped into the vaccine), care must be taken to avoid contamination. A needle should never contact the vaccine in a vial more than once.

SMALLPOX PREPAREDNESS AND RESPONSE PLANNING

A smallpox response plan has been in place in the United States since the early 1970s. In 1999, efforts were begun to update the response plan in the context of an intentional release of smallpox virus as an act of terrorism. Following the anthrax attacks in 2001 the plan was revised further to provide detailed information on surveillance and response to a smallpox virus release.

Smallpox Response Plan

- Key elements:
  - Surveillance and investigation of cases
  - Contact tracing
  - Isolation guidelines
  - Specimen collection and handling
  - Communications
  - Decontamination

The interim plan is intended to assist with local and state response planning by identifying actions that must be taken in the event of a suspected smallpox case. **The key elements of preparedness for smallpox response are surveillance and diagnosis to achieve the early detection of an introduced case; isolation of the case or cases; and identification and vaccination of the contacts of the case or cases**. Sections of the plan provide detailed information on these critical aspects of the plan, including surveillance and contact tracing, smallpox vaccine, isolation guidelines for both confirmed and suspected cases and febrile contacts of cases, specimen collection and transport, and decontamination, and communication.

In December 2002, the President announced a plan to better pro-

tect the American people against the threat of smallpox attack. Under the plan, the Department of Health and Human Services will work with state and local governments to form volunteer Smallpox Response Teams who can provide critical services in the event of a smallpox attack. To ensure that Smallpox Response Teams can mobilize immediately in an emergency, healthcare workers and other critical personnel may be asked to volunteer to receive the vaccine. The Department of Defense will also vaccinate certain military and civilian personnel who are or may be deployed in high threat areas. Some U.S. personnel assigned to certain overseas embassies may also be offered vaccination. The plan does not include a recommendation for vaccination of the general public.

Smallpox Response Teams

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

The current version of the Smallpox Response Plan and Guidelines, as well as information on Smallpox Response Team vaccination is available on the CDC smallpox website at http://www.cdc.gov/smallpox.

SELECTED REFERENCES

CDC. Vaccinia (smallpox) vaccine. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2001;50(RR-10):1-25.

CDC. Supplemental Recommendations on Adverse Events Following Smallpox Vaccine in the Pre-Event Vaccination Program: Recommendations of the Advisory Committee on Immunization Practices. *MMWR* 2003;52: 282-94.

Fenner F, Henderson DA, Arita I, et al (eds). *Smallpox and it's eradication*. Geneva: World Health Organization, 1988. Available from the World Health Organization website at http://www.who.int/emc/diseases/smallpox/Smallpoxeradication.htm

Frey S, Couch RB, Tacket CO, et al. Clinical responses to undiluted and diluted smallpox vaccine. *N Eng J Med* 2002;346:1265-74.

Halsell, J, et al. Myopericarditis following smallpox vaccination among vaccinia-naïve U.S. military personnel, *J Am Med Assoc* 2003;289:3283-9.

Henderson DA, Inglesby TV, Bartlett JG, et al. Smallpox as a biological weapon: medical and public health management. *J Am Med Assoc* 1999;281:2127-37.

Henderson DA, Borio LL, Lane JM. Smallpox and vaccinia. In: Plotkin SA, Orenstein WA, eds. *Vaccines.* 4th ed. Philadelphia, PA: Saunders; 2003:123-153.

Lane JM, Ruben FL, Neff JM, Millar JD. Complications of smallpox vaccination, 1968: national surveillance in the United States. *N Eng J Med* 1969;281:1201-8.

Lane JM, Ruben FL, Neff JM, Millar JD. Complications of small-

pox vaccination, 1968: results of ten statewide surveys. *J Infect Dis* 1970;122:303-39.

LeDuc JW, Jahrling PB. Strengthening national preparedness for smallpox: an update. *Emerg Infect Dis* 2001;7. Available on the CDC website at http://www.cdc.gov/ncidod/eid/vol7no1/leduc.htm

Mack TM. Smallpox in Europe, 1950-1971. *J Infect Dis* 1972;125:161-69.

Rosenthal SR, Merchlinsky M, Kleppinger C, Goldenthal KL. Developing new smallpox vaccines. *Emerg Infect Dis* 2001;7. Available on the CDC website at http://www.cdc.gov/ncidod/eid/vol7no6/rosenthal.htm

World Health Organization. Smallpox eradication: temporary retention of variola virus stocks. *Weekly Epidem Record* 2001;19:142-45.

Anthrax is a zoonotic disease caused by the spore-forming bacterium *Bacillus anthracis*. The term anthrax is derived from the Greek word for coal, *anthrakis*, because of the black skin lesions characteristic of the disease. A disease that appears to have been anthrax was described in the biblical book of Exodus as the fifth plague in about 1490 BCE. Descriptions of anthrax affecting both animals and humans are found in early Indian and Greek writings. An epidemic of anthrax in 17th century Europe caused an estimated 60,000 human deaths. The contagious nature of anthrax was described in 1823. *Bacillus anthracis* was first described in 1849, and was the first disease for which a microbial origin was definitively established, by Robert Koch in 1876. A live attenuated animal vaccine was developed and tested by Louis Pasteur in 1881. An improved animal vaccine containing a suspension of an avirulent, nonencapsulated live strain of *B. anthracis* was developed in 1939. The role of toxin in the pathogenesis of anthrax was demonstrated in 1954. A human vaccine composed of cell-free culture filtrate was developed in 1954, and an improved cell-free vaccine was licensed in the United States in 1970. Anthrax was first used effectively as a bioterrorist agent in 2001.

Anthrax

- Zoonotic disease caused by *Bacillus anthracis*
- Described in biblical times
- First animal vaccine developed by Louis Pasteur in 1881
- Used for bioterrorism in 2001

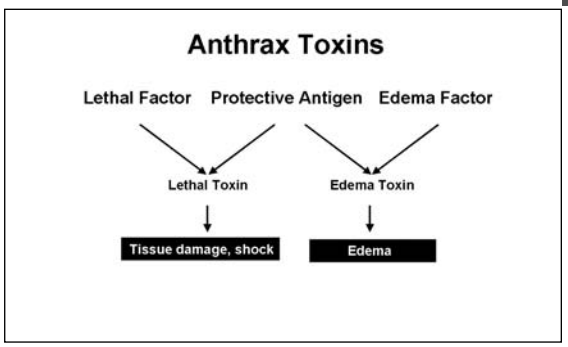
BACILLUS ANTHRACIS

B. anthracis is a large aerobic spore-forming gram-positive bacillus that grows well on common culture media, such as blood agar. Stained *B. anthracis* from culture media appears as long parallel chains of organisms with square ends, referred to as "boxcars." *B. anthracis* spores can remain viable and infective in the soil for many years, even decades. During this time, they are a potential source of infection for grazing livestock, but generally do not represent a direct infection risk for humans. Animals become infected when they ingest or inhale the spores while grazing. Humans can become infected with *B. anthracis* by skin contact, ingestion, or inhalation of *B. anthracis* spores originating from animal products of infected animals, or from inhalation of spores from the environment. Spores can be inactivated with sufficient contact with paraformaldehyde vapor, 5% hypochlorite or phenol solution, or by autoclaving.

Bacillus anthracis

- Gram-positive aerobic bacteria
- Spores may remain viable in soil for years
- Spores inactivated by paraformaldehyde vapor, hypochlorite, phenol, or autoclave
- Toxins responsible for tissue damage and edema

Anthrax spores germinate when they enter an environment rich in amino acids, nucleosides, and glucose, such as the blood or tissues of an animal. The replicating bacteria produce at least three proteins - protective antigen (PA), lethal factor (LF), and edema factor (EF). These proteins combine to form two toxins known as lethal toxin and edema toxin. PA and LF form lethal toxin, a protease that is believed to be responsible for tissue damage, shock and death, although the mechanism is not clear. PA and EF form edema toxin, an adenylate cyclase that upsets controls on ion and water transport across cell membranes and causes extensive edema.



PA binds to receptors on mammalian cells then binds with LF or EF. The toxin complexes are internalized to the endosome of the cell, then transported to the cytosol where they exert their effect.

PATHOGENESIS

Anthrax Pathogenesis

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

After wound inoculation or ingestion, macrophages engulf *B. anthracis* spores where the spores germinate. The vegetative bacteria produces a capsule that allows it to evade the immune system by resisting phagocytosis, and protects the organism from lysis by cationic proteins in the serum. Lethal toxin and edema toxin are produced. If not contained, the bacteria can spread to draining lymph nodes and intracellular space, leading to further production of toxins. The toxins result in necrosis of lymphatic tissue, which leads to the release of large numbers of bacteria. A bacteremia may ensue, and lead to overwhelming septicemia, widespread tissue destruction, organ failure, and death. In inhalation anthrax, spores are transported from the alveoli to the tracheobronchial and mediastinal lymph nodes. Lethal toxin and edema toxin are produced and cause tissue necrosis and extensive edema. Production of toxins leads to the massive hemorrhagic lymphadenitis and mediastinitis characteristic of inhalational disease.

Anthrax Pathogenesis

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

Studies in animals indicate that inhaled spores may not immediately germinate within the alveoli but reside there potentially for weeks, perhaps months, until taken up by alveolar macrophages. Spores then germinate and begin replication within the macrophages and lymphatic tissue. Antibiotics are effective against germinating or vegetative *B. anthracis* but are not effective against the nonvegetative or spore form of the organism. Consequently, disease development can be prevented as long as a therapeutic level of antibiotics is maintained to kill germinating *B. anthracis* organisms. After discontinuation of antibiotics, if the remaining nongerminated spores are sufficiently numerous to evade or overwhelm the immune system when they germinate, disease will then develop. This phenomenon of delayed onset of disease is not recognized to occur with cutaneous or gastrointestinal exposures.

Anthrax Clinical Features

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

CLINICAL FEATURES

The symptoms and incubation period of human anthrax are determined by the route of transmission of the organism. There are three clinical forms of anthrax: cutaneous, gastrointestinal, and inhalation.

CUTANEOUS ANTHRAX

Cutaneous Anthrax

- Incubation period 1-12 days
- Papule, then vesicle, then necrotic ulcer (eschar) with black center
- Usually painless
- Case-fatality:
  - –without antibiotics – 5%-20%
  - –with antibiotics - <1%

Most (>95%) naturally occurring *B. anthracis* infections are cutaneous and occur when the bacterium enters a cut or abrasion on the skin (e.g., when handling *B. anthracis*- contaminated animals, animal products, or other objects). The reported incubation period for cutaneous anthrax ranges from 0.5 to 12 days. Skin infection begins as a small papule that may be pruritic, progresses to a vesicle in 1-2 days, and erodes leaving a necrotic ulcer (eschar) with a characteristic black center. Secondary vesicles around the primary lesions may develop. The lesion is usually painless. Other symptoms may include swelling of adjacent lymph nodes, fever, malaise,

and headache. The diagnosis of cutaneous anthrax is suggested by the presence of the eschar, the presence of edema out of proportion to the size of the lesion, and the lack of pain during the initial phases of the infection. The case-fatality rate of cutaneous anthrax is 5% to 20% without antibiotic treatment and <1% with antibiotic treatment.

GASTROINTESTINAL ANTHRAX

The intestinal form of anthrax usually occurs after eating contaminated meat. The incubation period for intestinal anthrax is suspected to be 1-7 days. Involvement of the pharynx is characterized by lesions at the base of the tongue or tonsils, with sore throat, dysphagia, fever, and regional lymphadenopathy. Involvement of the lower intestine is characterized by acute inflammation of the bowel. Initial signs of nausea, loss of appetite, vomiting, and fever are followed by abdominal pain, vomiting of blood, and bloody diarrhea. The case-fatality rate of gastrointestinal anthrax is unknown but is estimated to be 25%-60%.

Gastrointestinal Anthrax

- Incubation period 1-7 days
- Pharyngeal involvement includes oropharyngeal ulcerations with cervical adenopathy and fever
- Intestinal involvement includes abdominal pain, fever, bloody vomiting or diarrhea
- Case-fatality estimated at 25-60%

INHALATION ANTHRAX

Originally known as woolsorter's disease, inhalation anthrax results from inhalation of 8,000-50,000 spores of *B. anthracis*. This form of anthrax would be expected to be the most common following an intentional release of *B. anthracis*. The incubation period for inhalation anthrax for humans appears to be 1-7 days, but may be as long as 43 days. The median incubation period for the first 10 bioterrorism-related inhalation anthrax cases in 2001 was 4 days, with a range of 4-6 days. However, the incubation period for inhalation anthrax may be inversely related to the dose of *B. anthracis*. Data from studies of laboratory animals suggest that *B. anthracis* spores continue to vegetate in the host for several weeks after inhalation, and antibiotics can prolong the incubation period for developing disease.

Inhalation Anthrax

- Incubation period: 1-7 days (range up to 43 days)
- Prodrome of cough, myalgia, fatigue, and fever
- Rapid deterioration with fever, dyspnea, cyanosis and shock, often with radiographic evidence of mediastinal widening
- Case fatality:
  - –without antibiotic treatment – 86%- 97%
  - –with antibiotic treatment - 75% (45% in 2001)

Initial symptoms of inhalation anthrax can include a nonproductive cough, myalgia, fatigue, and fever. Profound, often drenching sweat was a prominent feature of the first 10 bioterrorism-related cases in 2001. A brief period of improvement has been reported following the prodromal symptoms, but was not seen in the 2001 cases. Rapid deterioration then occurs, with high fever, dyspnea, cyanosis, and shock. Chest x-ray often shows pleural effusion and mediastinial widening due to lymphadenopathy. Meningitis, often hemorrhagic, occurs in up to half of patients with inhalation anthrax. Prior to the bioterrorist attacks in 2001, the case-fatality estimates without antibiotics were 85% - 97%. With antibiotics, the case-fatality rate is estimated to be 75%. For inhalation anthrax cases in 2001, the case-fatality rate with intensive therapy was 45% (5 of 11 cases). Death sometimes occurs within hours of onset.

Initial symptoms of an **influenza-like illness (ILI)** could be similar to early symptoms of inhalation anthrax. ILI is a nonspecific

respiratory illness characterized by fatigue, fever, cough, and other symptoms. Most cases of ILI are not caused by influenza, but by other viruses, such as rhinovirus and adenovirus. **Nasal congestion and rhinorrhea (runny nose) are common with ILI, but not common with inhalation anthrax. Shortness of breath is common with inhalation anthrax but not common with ILI**. Most persons with inhalation anthrax have abnormalities on chest x-ray, whereas most persons with ILI do not have abnormal chest x-rays (although primary influenza pneumonia or secondary bacterial pneumonia may occur in persons with influenza).

LABORATORY DIAGNOSIS

Anthrax Laboratory Diagnosis

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

The diagnosis of cutaneous anthrax should be suspected by the characteristic painless, shallow ulcer with a black crust. Gram stain of vesicular fluid will reveal typical gram-positive bacteria. Diagnosis can be confirmed by culture. Gastrointestinal anthrax is difficult to diagnosis because of its similarity to other severe gastrointestinal diseases. A history of ingesting potentially contaminated meat and typical symptoms may be helpful. Diagnosis of inhalation anthrax can also be difficult. Mediastinal widening on chest x-ray is a useful clinical finding. The bacterial burden may be so great in advanced infection that bacteria are visible on Gram stain of unspun peripheral blood. Gram-positive bacteria may be present in other clinical specimens, such as pleural fluid, skin biopsy lesion material, oropharyngeal ulcers, or cerebral spinal fluid. Diagnosis is usually confirmed with a positive culture for *B. anthracis*. Standard blood cultures should show growth in 6-24 hours. Other laboratory tests that may assist in the diagnosis are polymerase chain reaction (PCR), which detects *B. anthracis* DNA in pleural fluid or blood, serology (PA-based ELISA), and tissue immunohistochemistry, in which tissue is stained with specific cell wall and capsular antibodies.

MEDICAL MANAGEMENT

Anthrax Medical Management

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

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

Antibiotics are the most important therapeutic intervention in any form of anthrax, and should be started as soon as the disease is suspected. Naturally occurring strains of *B. anthracis* are typically sensitive to several antibiotics, including penicillin, tetracycline, and oral fluoroquinolones (ciprofloxacin and ofloxacin). *B. anthracis* produces a cephalosporinase that inhibits the antibacterial activity of cephalosporins such as ceftriaxone. Consequently, cephalosporins should not be used for treatment of anthrax. Naturally occurring *B. anthracis* may also be resistant to other commonly used antibiotics, such as sulfamethoxazole, trimethoprim, and aztreonam.

Survival of patients with bioterrorism-related inhalation anthrax was higher (55%) than in previous descriptions. All patients received combination antimicrobial therapy with more than one agent active against *B. anthracis*. The apparent improvement in survival suggests that the antibiotic combinations used in these patients may have therapeutic advantage compared to previous

regimens. Limited data on treatment suggests that early intravenous treatment with a fluoroquinolone (*e.g.*, ciprofloxacin) and at least one other active drug may improve survival. Treatment should initially be intravenous, then oral when clinically appropriate. Antibiotics should be continued for 30 to 60 days, or longer. In addition to antibiotics, survival of persons with inhalation anthrax appears to be more likely with aggressive supportive care, such as draining of pleural effusions, correction of electrolyte and acid-base disturbances, and early mechanical ventilation.

For cutaneous anthrax, ciprofloxacin or doxycycline is recommended as first line therapy. Intravenous therapy with a multidrug regimen is recommended for cutaneous anthrax with signs of systemic involvement, for extensive edema, or for lesions on the head and neck. Cutaneous anthrax is typically treated for 7-10 days. However, in the setting of a bioterrorism attack, the risk for simultaneous aerosol exposure may be high. As a result, persons with cutaneous anthrax associated with a bioterrorism attack should be treated for 60 days. Even if promptly treated with appropriate antibiotics, cutaneous anthrax will continue to progress through the eschar phase.

The most current recommendations on treatment of anthrax can be found on the CDC Public Health Emergency Preparedness and Response website at http://www.bt.cdc.gov.

EPIDEMIOLOGY

OCCURRENCE

Anthrax occurs worldwide and is most common in agricultural regions with inadequate control programs for anthrax in livestock. These regions include South and Central America, Southern and Eastern Europe, Asia, Africa, the Caribbean, and the Middle East. Prior to 2001, anthrax was very rare in the United States, with no human cases reported in 1993-2000.

Anthrax Epidemiology

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

RESERVOIR

The main reservoirs of anthrax are infected animals and the soil. Anthrax spores are highly resistant to physical and chemical agents and persist in the environment for many years. The spores may remain dormant in certain types of soil for decades.

TRANSMISSION

The most common method of transmission of anthrax is through direct contact with an infected animal. *B. anthracis* may enter the body through a pre-existing skin lesion or may be inadvertently introduced through an injury from a contaminated object. The result of this source of transmission is cutaneous anthrax. Vectors such as flies and vultures may mechanically spread the organism in some circumstances, but vectors are not believed to be important

in human infection. Meat from an infected animal can transmit *B. anthracis* if the infected meat is eaten undercooked.

B. anthracis can also be transmitted by **inhalation of airborne or aerosolized spores**. In nature, *B. anthracis* spores are 2-6 microns in diameter. If aerosolized by industrial processing of contaminated products, or as a result of a bioterrorist attack, particles >5 microns in diameter quickly fall from the atmosphere and bond to any surface. These particles are difficult to resuspend in the air, but may remain in the environment for years. Spores 2-5 microns in diameter behave as a gas and move through the environment without settling. Spores of this size are able to pass through the pores in paper, as occurred in mail processing facilities subsequent to the anthrax attacks in 2001. Particles <5 microns in diameter, if inhaled, are small enough to reach the lower respiratory tract and can lead to inhalation anthrax.

Anthrax Epidemiology

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

Naturally-occurring anthrax is extremely rare in the United States (see Secular Trends, below). Persons at risk of anthrax are primarily those who have contact with infected animals. Although animal anthrax occurs in the United States, this mode of transmission is rare. Laboratory personnel or other persons who come into contact with *B. anthracis* spores could be at increased risk, although only two laboratory-associated anthrax cases have been reported (both had inhalation anthrax). In the past, persons involved in the processing of wool, hair, hides, and/or bones from infected animals could be infected. However, improvements in animal husbandry and strict importation requirements for animal products have made this source of infection extremely rare. Exposure to *B. anthracis* through an effective bioterrorist attack occurred for the first time in 2001.

TEMPORAL PATTERN

Anthrax may occur throughout the year. Animal-related cases occur primarily in the spring and summer.

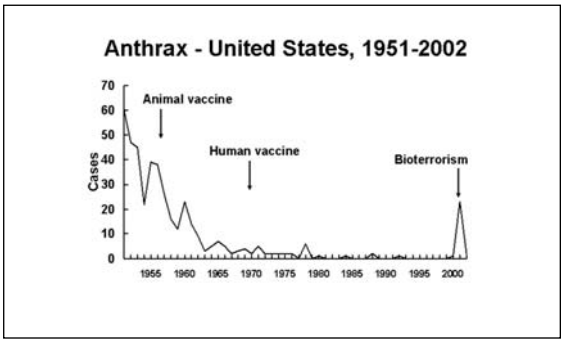
COMMUNICABILITY

Persons with inhalation anthrax are not contagious. Human-to-human transmission of cutaneous anthrax has been reported but is very rare.

SECULAR TRENDS

Anthrax most commonly occurs in herbivores, which are infected by ingesting or inhaling spores from the soil. Humans are infected naturally following contact with anthrax-infected animals or anthrax-contaminated animal products. Estimation of the true incidence of human anthrax worldwide is difficult because reporting of anthrax cases is unreliable. The largest recent epidemic of human anthrax occurred in Zimbabwe during 1978-1980; 9,445 cases occurred, including 141 (1.5%) deaths.

In the United States, the annual incidence of human anthrax declined from approximately 130 cases annually in the early 1900s to no cases during 1993-1999. A single case of cutaneous anthrax was reported in 2000, and was associated with an outbreak of anthrax in farm animals in North Dakota. Most cases reported in the United States have been cutaneous. During the 20th century, only 18 cases of inhalation anthrax were reported, the most recent in 1976. Gastrointestinal anthrax has not been reported in the United States.



Anthrax continues to be reported among domestic and wild animals in the United States. The incidence of anthrax in U.S. animals is unknown. However, reports of animal infection have occurred in the Great Plains states from Texas to North Dakota.

Except the single case in 2000, all cases of anthrax in the United States since 1993 were related to intentional exposure from a bioterrorist attack. A total of 22 cases (11 inhalation, 11 cutaneous) were reported from Florida, New Jersey, Connecticut, New York City, and the District of Columbia in October and November 2001. *B. anthracis* was contained in at least 2 envelopes sent through the U.S. postal system. Most cases were exposed in mail sorting facilities or had direct contact with a contaminated envelope. Cross-contamination of mail in sorting facilities is suspected as the source for cases without known exposure to a contaminated facility or envelope. The source of the *B. anthracis* used in these attacks has not been determined.

Anthrax Bioterrorism Attacks – United States, 2001

- 22 cases (11 inhalation, 11 cutaneous) in 4 states and DC
- *B. anthracis* sent through U.S. mail
- Most exposures occurred in mail sorting facilities and sites where mail was opened

CASE DEFINITION

A **confirmed case of anthrax** is defined as a clinically compatible case of cutaneous, respiratory, or gastrointestinal illness that is laboratory confirmed by isolation of *B. anthracis* from an affected tissue or site, or other laboratory evidence of *B. anthracis* infection based on at least two supportive laboratory tests. A **suspect case of anthrax** is a clinically compatible case of illness without isolation of *B. anthracis* and no alternative diagnosis, but with laboratory evidence of *B. anthracis* by one supportive laboratory test, or a clinically compatible case of anthrax epidemiologically linked to a confirmed environmental exposure, but without corroborative laboratory evidence of *B. anthracis* infection.

Any person suspected of having any type of anthrax must be reported immediately to the local or state health department.

ANTHRAX VACCINE

Louis Pasteur successfully attenuated *B. anthracis* and produced the first live attenuated bacterial vaccine for animals in 1881. An improved live vaccine containing an unencapsulated avirulent variant of *B. anthracis* (the Stern vaccine) was developed for livestock in 1939. This vaccine continues to be used as the principal veteri-

Anthrax Vaccines

- 1881 Pasteur develops first live attenuated veterinary vaccine for livestock
- 1939 Improved live veterinary vaccine
- 1954 First cell-free human vaccine
- 1970 Improved cell-free vaccine licensed

nary vaccine in the Western Hemisphere. The use of livestock vaccines was associated with occasional death in the animal, and live vaccines were considered unsuitable for humans. In the early twentieth century filtrates of artificially cultivated *B. anthracis* were explored as potential vaccines. The first human culture filtrate vaccine was developed in 1954. This vaccine used alum as an adjuvant. It provided protection in monkeys, caused minimal reactivity and short-term adverse reactions in humans, and was used in the only efficacy study of human vaccination against anthrax in the United States. In the late 1950s the vaccine was improved through the selection of a *B. anthracis* strain that produced a higher fraction of protective antigen, the production of a protein-free media, and the use of aluminum hydroxide rather than alum as the adjuvant. This vaccine - anthrax vaccine adsorbed (AVA) - was licensed for use in the United States in 1970.

CHARACTERISTICS

AVA is the only FDA-licensed human anthrax vaccine in the United States. It is prepared from a cell-free culture filtrate of a toxigenic, nonencapsulated strain of *B. anthracis*. The vaccine does not contain dead or live bacteria. The filtrate contains a mix of cellular products and contains all three toxin components (LF, EF, and PA). The vaccine is adsorbed to aluminum hydroxide as adjuvant. AVA contains no more that 0.83 mg aluminum per 0.5 mL dose, 0.0025% benzethonium chloride as a preservative, and 0.0037% formaldehyde as a stabilizer.

Anthrax Vaccine

- Cell-free culture filtrate of toxigenic strain of *B. anthracis*
- Filtrate contains protective antigen (PA) and other cellular products
- Adsorbed to aluminum hydroxide as an adjuvant
- Contains small amounts of benzethonium chloride (preservative) and formaldehyde (stabilizer)

IMMUNOGENICITY AND VACCINE EFFICACY

The principal antigen responsible for producing immunity is PA. Approximately 83% of recipients of AVA develop detectable antibody to PA by 2 weeks after the first dose and in 91% of vaccinees who received two or more doses. Approximately 95% of vaccinees seroconvert with a fourfold rise in anti-PA IgG titers after three doses. However, the precise correlation between antibody titer (or concentration) and protection against infection is not known with certainty.

Anthrax Vaccine Efficacy

- 95% seroconversion following 3 doses
- One controlled human trial using earlier vaccine
  - –92.5% efficacy (cutaneous and inhalation disease combined)
- Animal models suggest protection against inhalation anthrax
- Duration of immunity unknown

The only controlled clinical human trial of anthrax was performed among mill workers in 1955-1959 using the alum-precipitated vaccine (the PA-based precursor to the currently licensed AVA). In this controlled study, 379 employees received the vaccine, 414 received a placebo, and 340 received neither the vaccine nor the placebo. This study documented **a vaccine efficacy of 92.5% for protection against anthrax** (cutaneous and inhalation combined). During the study, an outbreak of inhalation anthrax occurred among the study participants. Overall, five cases of inhalation anthrax occurred among persons who were either placebo recipients or did not participate in the controlled part of the study. No cases occurred in anthrax vaccine recipients. No data are available regarding the efficacy of anthrax vaccine for persons aged <18 years and >65 years.

The protective efficacy of the alum-precipitated vaccine (the earlier form of the PA filtrate vaccine) and AVA have been demonstrated in several animal studies using different routes of spore exposure. Inhalation anthrax in macaque (Rhesus) monkeys is believed to best reflect human disease, and AVA has been shown to be protective for up to 100 weeks after pulmonary challenge with *B. anthracis*.

The duration of immunity in humans following vaccination with AVA is unknown. Data from animal studies suggest that the duration of efficacy after two inoculations might be 1-2 years.

Anthrax Vaccine Efficacy in Macaques

Year	Vaccine	Challenge	Time	Survival
1954	alum	50 x LD50	16 d	7 of 7
1954	alum	100 x LD50	16 d 34 d	4 of 4 4 of 4
1956	alum	100 x LD50	7 d 1 yrs 2 yrs	10 of 10 10 of 10 6 of 7
1995	alum. hyd.	200 x LD50	8 wks 38 wks 100 wks	10 of 10 3 of 3 7 of 8
1995	alum. hyd.	200 x LD50	12 wks	10 of 10

VACCINATION SCHEDULE AND USE

Primary vaccination with AVA consists of three subcutaneous (SC) injections at 0, 2, and 4 weeks, followed by doses at 6, 12, and 18 months. To maintain immunity, the manufacturer recommends an annual booster dose. The basis for the schedule of vaccinations at 0, 2, and 4 weeks, and 6, 12, and 18 months followed by annual boosters is not well defined.

Anthrax Vaccine Schedule

- Initial doses at 0, 2, and 4 weeks
- Additional doses at 6, 12, and 18 months
- Annual booster doses thereafter
- Alternative schedules being investigated

As with other licensed vaccines, no data indicate that increasing the interval between doses adversely affects immunogenicity or safety. **Interruption of the vaccination schedule does not require restarting the entire series of anthrax vaccine or the addition of extra doses**.

Because of the complexity of a six-dose primary vaccination schedule and frequency of local injection-site reactions (see Adverse Reactions), studies are being conducted to assess the immunogenicity of schedules with a reduced number of doses and with intramuscular (IM) administration rather than subcutaneous administration. Preliminary results indicate that schedules using fewer doses at longer intervals, and IM rather than SC route produce similar concentrations of antibody to PA. However, **no alternate schedule has yet been approved for use by the FDA**.

PRE-EXPOSURE VACCINATION

Anthrax Vaccine Pre-exposure Vaccination

- Persons working with production quantities or concentrations of *B. anthracis* cultures
- Persons engaged in activities with a high potential for production of aerosols containing *B. anthracis*
- Persons with increased risk of exposure to intentional release of *B. anthracis* (e.g., certain military personnel)

Routine pre-exposure vaccination with AVA is indicated for **persons engaged in work involving production quantities or concentrations of *B. anthracis* cultures and in activities with a high potential for aerosol production**. Laboratory personnel using standard Biosafety Level 2 practices in the routine processing of clinical samples are not at increased risk for exposure to *B. anthracis* spores. The risk for persons who come in contact in the workplace with imported animal hides, furs, bone meal, wool, animal hair, or bristles has been reduced by changes in industry standards and import restrictions. Routine pre-exposure vaccination is recommended only for persons in this group for whom these standards and restrictions are insufficient to prevent exposure to anthrax spores. Routine vaccination of veterinarians in the United States is not recommended because of the low incidence of animal

cases. However, vaccination might be indicated for veterinarians and other high-risk persons handling potentially infected animals in areas with a high incidence of anthrax cases.

Pre-exposure vaccination may be indicated for certain military personnel and other select groups who may be exposed to an intentional release of *B. anthracis*. Pre-exposure vaccination is not currently recommended for emergency first responders, federal responders, medical practitioners, or private citizens.

POSTEXPOSURE VACCINATION

Anthrax Vaccine
Postexposure Vaccination

- No efficacy data for postexposure vaccination of humans
- Postexposure vaccination alone not effective in animals
- Combination of vaccine and antibiotics appears effective in animal model

Limited data are available regarding the postexposure efficacy of AVA. **Studies in nonhuman primates indicate that postexposure vaccination alone is not protective**. However, studies have shown that **antibiotics in combination with postexposure vaccination are effective at preventing disease in animals after exposure to *B. anthracis* spores**. The current vaccine is approved by FDA only for pre-exposure vaccination. The optimal number of doses for postexposure prophylaxis use of the vaccine is not known. An estimated 83% of human vaccinees develop a vaccine-induced immune response after two doses of the vaccine and >95% develop a fourfold rise in antibody titer after three doses. Although the precise correlation between antibody titer and protection against disease is not clear, these studies of postexposure vaccine regimens used in combination with antibiotics in nonhuman primates have consistently documented that one or two doses of vaccine were sufficient to prevent development of disease once antibiotics were discontinued.

Anthrax Postexposure Prophylaxis
Vaccine Combined with Antibiotics

- Henderson, et al (1956): earlier PA-based vaccine
  - Methods: 5 days of penicillin compared to penicillin plus postexposure vaccination
  - Results: 9 of the 10 receiving just penicillin died, while all of the macaques receiving both penicillin and vaccine survived
- Friedlander et al (1993): aluminum hydroxide PA filtrate vaccine (current FDA-licensed vaccine)
  - Methods: 30 days of various antibiotics compared to 30 days of doxycycline plus postexposure vaccination
  - Results: 9 of the 10 animals in the doxycycline-alone arm survived, while all receiving doxycycline and vaccine survived

ADVERSE REACTIONS FOLLOWING VACCINATION

The most common adverse reactions following AVA are local reactions. In AVA prelicensure evaluations, minor local reactions (defined as erythema, edema, and induration <30 mm) occurred after 20% of vaccinations, moderate local reactions (edema and induration of 30 mm - 120 mm) occurred after 3% of vaccinations, and severe local reactions (edema or induration >120 mm) occurred after 1% of vaccinations. Local reactions usually occur within 24 hours and subside within 48 hours. Subcutaneous nodules occur at the injection site in 30%-50% of recipients and persist for several weeks. In multiple Department of Defense studies, systemic reactions (*i.e.*, chills, muscle aches, malaise, or nausea) occurred in 5%-35% of vaccine recipients. Systemic reactions are usually mild and transient. Fever is not common following AVA. Severe reactions (*e.g.*, allergic) are rare.

Anthrax Vaccine Adverse Reactions

• Local reactions	
– minor	20%-50%
– severe	1%
• Systemic symptoms	5%-35%
• Severe reactions	rare

Adverse reactions following anthrax vaccination have been assessed in several studies conducted by the Department of Defense in the context of the routine anthrax vaccination program. In one of these studies, 1.9% of vaccine recipients reported limitations in work performance or had been placed on limited duty due to a local reaction. Only 0.3% reported >1 day lost from work; 0.5% consulted a clinic for evaluation; and one person (0.02%) required

hospitalization for an injection-site reaction. Adverse reactions were reported more commonly among women than among men.

No studies have documented occurrence of chronic diseases (*e.g.*, cancer or infertility) following anthrax vaccination. In an assessment of the safety of anthrax vaccine, the Institute of Medicine (IOM) noted that published studies reported no significant adverse effects of the vaccine, but the literature is limited to a few short-term studies. One published follow-up study of laboratory workers at Fort Detrick, Maryland, concluded that during the 25-year period following receipt of anthrax vaccine, the workers did not develop any unusual illnesses or unexplained symptoms associated with vaccination. The IOM found no evidence that people face an increased risk of experiencing life-threatening or permanently disabling adverse reactions immediately after receiving AVA, when compared with the general population. Nor did it find any convincing evidence that people face elevated risk of developing long term adverse health effects, although data are limited in this regard (as they are for all vaccines).

CDC has conducted two epidemiologic investigations of the health concerns of Persian Gulf War (PGW) veterans that examined a possible association with several factors, including anthrax vaccination. **Current scientific evidence does not support an association between anthrax vaccine and PGW illnesses**.

No data are available regarding the safety of anthrax vaccine for persons aged <18 years and >65 years.

Adverse reactions can occur in persons who must complete the anthrax vaccination series because of high risk of exposure or because of employment requirements. Several protocols have been developed to manage specific local and systemic adverse reactions (available at www.anthrax.osd.mil). However, these protocols have not been evaluated in randomized trials.

CONTRAINDICATIONS AND PRECAUTIONS

As with all vaccines, AVA is **contraindicated for persons who have experienced a severe allergic (anaphylactic) reaction to a vaccine component or following a prior dose of AVA.** Anthrax vaccine is **contraindicated in persons who have recovered from anthrax** because of observations of more severe adverse reactions among recipients with a vaccine history of anthrax than among nonrecipients. **A moderate or severe acute illness** is a precaution, and vaccination should be postponed until recovery. This prevents superimposing the adverse effects of the vaccine on the underlying illness or mistakenly attributing a manifestation of the underlying illness to the vaccine. Vaccine can be administered to persons who have mild illnesses with or without low-grade fever.

No studies have been published regarding use of anthrax vaccine among pregnant women. The vaccine is neither

Anthrax Vaccine
Precautions and Contraindications

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

licensed nor recommended during pregnancy. Pregnant women should be vaccinated against anthrax only if the potential benefits of vaccination outweigh the potential risks to the fetus. No data suggest increased risk for side effects or temporally related adverse events associated with receipt of anthrax vaccine by breastfeeding women or breastfed children. AVA may be administered to an **immunosuppressed person** if necessary, but response to the vaccine may be suboptimal.

VACCINE STORAGE AND HANDLING

AVA must be stored at 2°- 8°C (35°- 46°F). The vaccine should not be frozen. The manufacturer (Bioport Corporation, Lansing, Michigan) should be contacted for advice should the vaccine be exposed to freezing temperature or a prolonged period at room temperature.

POSTEXPOSURE PROPHYLAXIS WITH ANTIBIOTICS

Anthrax Postexposure Antibiotic Prophylaxis

- Ciprofloxicin, doxycycline, and procaine penicillin G approved for postexposure prophylaxis after aerosol exposure to *B. anthracis*
- Due to latency of spores in lung, antibiotics should continue for 30-60 days or more
- Discontinue antibiotics after third dose of vaccine

Procaine penicillin G, ciprofloxacin, and doxycycline are approved by FDA for the treatment of anthrax and are considered the drugs of choice for the treatment of naturally occurring anthrax. In addition, ofloxacin has also demonstrated in vitro activity against *B. anthracis*. Although naturally occurring *B. anthracis* resistance to penicillin is rare, such resistance has been reported.

Antibiotics are effective against the germinated form of *B. anthracis* but are not effective against the spore form of the organism. Following inhalation exposure, spores can survive in tissues for months without germination in nonhuman primates. This phenomenon of delayed vegetation of spores resulting in prolonged incubation periods has not been observed for routes of infection other than inhalation. In one study, macaques were exposed to four times the LD50 dose of anthrax spores (the dose of spores that will result in the death of 50% of the exposed animals). The proportion of spores that survived in the lung tissue was estimated to be 15%-20% at 42 days, 2% at 50 days, and <1% at 75 days. Spores have been detected in animals up to 100 days following exposure. Although the LD50 dose for humans is believed to be similar to that for nonhuman primates, the length of persistence of *B. anthracis* spores in human lung tissue is not known. The length of persistence probably depends on the dose inhaled. The prolonged incubation period reported in an outbreak of inhalation anthrax in the Soviet Union suggests that lethal amounts of spores might have persisted up to 43 days after initial exposure.

POSTEXPOSURE PROPHYLAXIS FOLLOWING INHALATION EXPOSURE

Postexposure prophylaxis against *B. anthracis* with antibiotics is recommended following an aerosol exposure to *B. anthracis* spores. Such exposure might occur following an inadvertent exposure in a laboratory setting or a biological terrorist incident. Inhalation

anthrax in humans has not been reported to result from contact with naturally occurring anthrax among animals. Currently, **ciprofloxacin, doxycycline, and procaine penicillin G** are approved by FDA for use as antimicrobial prophylaxis for inhalation *B. anthracis* infection. Because of concern about the possible antibiotic resistance of *B. anthracis*, ciprofloxacin or doxycycline should be used initially for antibiotic prophylaxis until organism susceptibilities are known. Antibiotic chemoprophylaxis can be switched to penicillin VK or amoxicillin, particularly for children, once antibiotic susceptibilities are known and the organism is found to be penicillin susceptible with minimum inhibitory concentrations (MICs) attainable with oral therapy.

Because of the potential persistence of spores following an aerosol exposure, **antibiotic therapy should be continued for at least 60 days if used alone**. If vaccine is available, antibiotics can be discontinued after three doses of vaccine have been administered according to the standard schedule (0, 2, and 4 weeks). Although the shortened (3 dose) vaccine regimen has been effective when used in a postexposure regimen that includes antibiotics, the duration of protection after vaccination is not known. Therefore, if subsequent exposures occur, additional vaccinations might be required.

Recommended Postexposure Prophylaxis to Prevent Inhalational Anthrax

	Initial Therapy	Duration
Adults (including pregnant women and immunocompromised)	Ciprofloxacin 500 mg PO BID OR Doxycycline 100 mg PO BID	60 days
Children	Ciprofloxacin 10-15 mg/kg PO Q 12 hrs* OR Doxycycline: >8 yrs and >45 kg: 100 mg PO BID; >8 yrs and ≤45 kg: 2.2 mg/kg PO BID; ≤8 yrs: 2.2 mg/kg PO BID	60 days

*Ciprofloxacin dose should not exceed 1 gram per day in children.

POSTEXPOSURE ANTIBIOTIC PROPHYLAXIS FOLLOWING CUTANEOUS OR GASTROINTESTINAL EXPOSURE

No controlled studies have been conducted in animals or humans to evaluate the use of antibiotics alone or in combination with vaccination following cutaneous or gastrointestinal exposure to *B. anthracis*. Cutaneous and rare gastrointestinal exposures of humans are possible following outbreaks of anthrax in livestock. In these situations, on the basis of pathophysiology, reported incubation periods, current expert clinical judgment, and lack of data, postexposure prophylaxis might consist of antibiotic therapy for 7-14 days. Antibiotics could include ciprofloxacin, ofloxacin, doxycycline, penicillin, or amoxicillin.

BIOTERRORISM PREPAREDNESS

Research on anthrax as a biological weapon began more than 90 years ago. In 1999, at least 17 nations were believed to have offensive biological weapons programs; it is not known how many are working with anthrax. Iraq has acknowledged producing and weaponizing anthrax. One terrorist group, Aum Shinrikyo, dispersed aerosols of anthrax and botulism throughout Tokyo, Japan, on at least 8 occasions. For unknown reasons the attacks failed to produce illness.

Anthrax in Biological Terrorism

- ***B. anthracis*** **considered likely biological terrorism threat**
  - **–aerosolized stable spore form**
  - **–human LD50 8,000 to 40,000 spores (one deep breath at site of release)**
  - **–acute illness with high fatality rate**

B. anthracis is considered one of the most likely biological warfare agents because of the ability of *B. anthracis* spores to be transmitted by the respiratory route, the high mortality of inhalation anthrax, and the greater stability of *B. anthracis* spores compared with other

potential biological warfare agents. The World Health Organization estimates that 50 kg of *B. anthracis* released upwind of a population center of 500,000 could result in 95,000 deaths and 125,000 hospitalizations, far more deaths than predicted in any other scenario of agent release.

A total of 22 anthrax cases in four states and the District of Columbia occurred in October and November 2001 as a result of a series of bioterrorist attacks with *B. anthracis*. Eleven cases were inhalation anthrax, of which 5 were fatal. The organism was sent through the U.S. postal system. Nine of the cases of inhalation anthrax occurred in persons with direct exposure to an envelope containing *B. anthracis*. The envelopes contaminated several office buildings and mail processing centers. Cross-contamination of mail in the processing centers is suspected as the source of exposure in those cases without known direct exposure to a contaminated letter. Several thousand persons required postexposure antibiotic prophylaxis because of exposure to contaminated buildings.

Information about anthrax and bioterrorism preparedness

http://www.bt.cdc.gov

Information on the 2001 anthrax attacks, recommendations for management of anthrax infection and exposure, and information on bioterrorism preparedness is available on the CDC Public Health Emergency Preparedness and Response website at http://www.bt.cdc.gov.

SELECTED REFERENCES

Brachman PS, Friedlander AM, Grabenstein JD. In: Plotkin SA, Orenstein WA, eds. *Vaccines*. 4th ed. Philadelphia, PA: Saunders; 2003:887-904.

CDC. Use of anthrax vaccine in the United States. Recommendations of the Advisory Committee on Immunization Practices. *MMWR* 2000;49(RR-15):1-20.

CDC. Update: investigation of anthrax associated with intentional exposure and interim public health guidelines, October 2001. *MMWR* 2001;50:889-93.

CDC. Update: investigation of bioterrorism-related anthrax and interim guidelines for exposure management and antimicrobial therapy, October 2001. *MMWR* 2001;50:909-19.

CDC. Update: investigation of bioterrorism-related anthrax - Connecticut, 2001. *MMWR* 2001;50:1077-9.

Cieslak TJ, Eitzen EM. Clinical and epidemiologic principles of anthrax. *Emerg Infect Dis* 1999;5:552-5.

Demicheli V, Rivetti D, Deeks JJ, et al. The effectiveness and safety of vaccines against human anthrax: a systematic review. *Vaccine* 1998;16:880-4.

Inglesby TV, Henderson DA, Bartlett JG, et al. Anthrax as a bio-

logical weapon. *J Am Med Assoc* 1999;281:1735-45.

Jernigan JA, Stephens DS, Ashford DA. Bioterrorism-related inhalational anthrax: the first 10 cases reported in the United States. *Emerg Infect Dis* 2001;7:933-44.

Joellenbeck LM, Zwanziger L, Durch JS, et al (eds). *The anthrax vaccine: is it safe? Does it Work?* Washington DC:National Academy Press, March 2002. (Institute of Medicine Report)

LaForce MF. Anthrax. *Clin Infect Dis* 1994;19:1009-14.

Turnbull PCB. *Guidelines for the surveillance and control of anthrax in humans and animals*. Geneva, Switzerland: World Health Organization, Department of Communicable Diseases Surveillance and Response, 1998; publication no. WHO/EMC/ZDI./98.6.

Young JAT, Collier RJ. Attacking anthrax. *Sci Amer* 2002;286:48-59.