EPIDEMIOLOGY AND PREVENTION OF VACCINE-PREVENTABLE DISEASES

14TH EDITION

This book was produced by the Communication and Education Branch, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention. It was printed and distributed by the Public Health Foundation. For additional copies, contact the Public Health Foundation at 877-252-1200 or website http://bookstore.phf.org/.

The most current, 508-compliant version of this book is available at CDC's Pink Book website: https://www.cdc.gov/vaccines/pubs/pinkbook/index.html.

E-mail address for comments, questions, or suggestions about the contents of this book: nipinfo@cdc.gov.

Edited by:

Elisha Hall, PhD, RD

A. Patricia Wodi, MD

Jennifer Hamborsky, MPH, MCHES®

Valerie Morelli

Sarah Schillie, MD, MPH, MBA

Layout and Design by:

Peggy Dana

U.S.Department of Health and Human Services
Centers for Disease Control and Prevention

Table of Contents

On the cover

This illustration depicts *Bordetella pertussis*.

Graphic from the Public Health Image Library.

Suggested Citation:
Centers for Disease Control and Prevention. Epidemiology and Prevention of Vaccine-Preventable Diseases. Hall E., Wodi A.P., Hamborsky J., et al., eds. 14th ed. Washington, D.C. Public Health Foundation, 2021.

The editors would like to thank Skip Wolfe, who thoughtfully conceived, executed, and managed the Pink Book appendices.

The editors would also like to thank Dr. Kathy Towers-Solis for supporting the Pink Book through each new edition and promoting its importance for the public health workforce providing immunizations.

Finally, the editors would like to thank Dr. William L. Atkinson, who summarized, standardized, and compiled CDC's vaccine-preventable disease and vaccine teaching materials to create the Pink Book.

"He just thought it up and did it." – Apocalypse Now

Milestones in the History of Vaccination

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

Table of Contents

Milestones in the History of Vaccination

1870	1884-85	1900	1901	1909
Louis Pasteur creates the first live, attenuated bacterial vaccine (chicken cholera)	Pasteur creates the first live, attenuated viral vaccine for use in humans	Paul Ehrlich formulates receptor theory of immunity	First Nobel Prize in Medicine to von Behring for diphtheria antitoxin	Theobald Smith discovers a method for inactivating diphtheria toxin

Table of Contents

Milestones in the History of Vaccination

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

1923
First whole-cell pertussis vaccine tested

Gaston Ramon develops diphtheria toxoid

1926
Ramon and Christian Zoeller develop tetanus toxoid

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

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

Milestones in the History of Vaccination

1948	***1954***	***1955***	***1961***	***1963***
John Enders and colleagues isolate Lansing Type II poliovirus in human cell line	Enders and Peebles isolate measles virus Francis Field Trial of inactivated polio vaccine	Inactivated polio vaccine licensed	Human diploid cell line developed	Measles vaccine licensed Trivalent oral polio vaccine licensed

Table of Contents

Milestones in the History of Vaccination

1965	1966	1967	1969	1971
Bifurcated needle for smallpox vaccine licensed	World Health Assembly calls for global smallpox eradication	Maurice Hilleman develops Jeryl Lynn strain of mumps virus	Stanley Plotkin develops RA 27/3 strain of rubella vaccine virus	MMR vaccine licensed

15 Mumps

16 Pertussis

Milestones in the History of Vaccination

1977	***1979***	***1981***	***1983***	***1986***
Last indigenous case of smallpox (Somalia)	Last wild poliovirus transmission in the U.S.	First hepatitis B vaccine licensed	Smallpox vaccine withdrawn from civilian market	First recombinant vaccine licensed (hepatitis B) National Childhood Vaccine Injury Act passed

Table of Contents

Milestones in the History of Vaccination

1989	1990	1994	1995	1996
Two-dose measles vaccine recommendation	First polysaccharide conjugate vaccine licensed (*Haemophilus influenzae* type b)	Polio elimination certified in the Americas Vaccines for Children program begins	Varicella vaccine licensed Hepatitis A vaccine licensed First harmonized childhood immunization schedule published	Acellular pertussis vaccine licensed for infants

20 Rubella

21 Tetanus

Milestones in the History of Vaccination

1997	1998	1999	2000	2003
Sequential polio vaccination recommended	First rotavirus vaccine licensed	Exclusive use of inactivated polio vaccine recommended Rotavirus vaccine withdrawn	Pneumococcal conjugate vaccine licensed for infants	Live attenuated influenza vaccine licensed

Table of Contents

Milestones in the History of Vaccination

2004	***2004***	***2005***	***2005***	***2006***
Inactivated influenza vaccine recommended for all children 6–23 months of age	Indigenous transmission of rubella virus interrupted	Acellular pertussis vaccines licensed for adolescents and adults	MMR-varicella (MMRV) licensed	Second generation rotavirus vaccine licensed

Milestones in the History of Vaccination

2006	2006	2009	2010	2013
First human papillomavirus vaccine licensed	First herpes zoster vaccined licensed	H1N1 influenza pandemic declared	Influenza vaccine recommended for all persons 6 months and older	First quadrivalent influenza vaccine licensed

Appendices

Note: Appendices are periodically updated. For the most recent versions, refer to the appendices found online at: https://www.cdc.gov/vaccines/pubs/pinkbook/appendix/index.html

Milestones in the History of Vaccination

2014	2014	2017	2020	2020
First serogroup B meningococcal vaccine licensed	First 9-valent recombinant protein subunit HPV vaccine licensed	First recombinant zoster vaccine licensed 2-dose HepB vaccine using a novel adjuvant licensed	World Health Organization declares COVID-19 pandemic	FDA authorizes the first COVID-19 vaccine through Emergency Use Authorization

A. Patricia Wodi, MD and Valerie Morelli, BA

Immunology and Vaccine-Preventable Diseases

To understand how vaccines work and the foundation of recommendations for their use, it is helpful to understand the basic function of the human immune system. The following description is simplified; many excellent immunology textbooks provide additional detail.

Immunity is the ability of the human body to tolerate the presence of material indigenous to the body and to eliminate foreign substances. This discriminatory ability to eliminate foreign substances is performed by a complex system of interacting cells called the immune system. Since most organisms (e.g., bacteria, viruses, and fungi) are identified as foreign, the ability to identify and eliminate these substances provides protection from infectious diseases. Immunity is generally specific to a single organism or group of closely related organisms.

The immune system develops a defense against antigens, which are substances that can stimulate the immune system. This defense is known as the immune response and usually involves the production of:

- Protein molecules (immunoglobulins or antibodies, the major component of humoral immunity) by B-lymphocytes (B-cells)
- Specific cells, including T-lymphocytes (also known as cell-mediated immunity)

The most effective immune responses are generally produced in response to antigens present in a live organism. However, an antigen does not necessarily have to be present in a live organism to produce an immune response. Some antigens, such as hepatitis B surface antigen, are easily recognized by the immune system and produce adequate protection even if they are not carried on the live hepatitis B virus. Other materials are less effective antigens, and the immune response they produce may not provide good protection.

NOTES

NOTES

Types of Immunity

There are two basic mechanisms for acquiring immunity: passive and active.

Passive Immunity

Passive immunity is protection by antibody or antitoxin produced by one animal or human and transferred to another. Passive immunity provides immediate protection against infection, but that protection is temporary. The antibodies will degrade during a period of weeks to months, and the recipient will no longer be protected.

The most common form of passive immunity is that which an infant receives from the mother. Antibodies, specifically the class of antibody referred to as IgG, are transported across the placenta, primarily during the last 1 to 2 months of pregnancy. As a result, a full-term infant will have the same type of antibodies as the mother. These antibodies can protect the infant from certain diseases within the first few months after birth. Maternal antibodies provide better protection from some diseases (e.g., measles, rubella, tetanus) than from others (e.g., polio, pertussis).

Passive immunity can also be acquired through the transfusion of blood products. Some blood products (e.g., washed or reconstituted red blood cells) contain a relatively small amount of antibody, while some (e.g., intravenous immune globulin and plasma products) contain a large amount.

In addition to blood products used for transfusion, there are three other major sources of antibody used in human medicine. These are homologous pooled human antibody, homologous human hyperimmune globulin, and heterologous hyperimmune serum.

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

Homologous human hyperimmune globulins are antibody products that contain high titers of antibody targeting more specific antigens. These products are made from donated human plasma with high levels of the antibody of interest. Since hyperimmune globulins are from humans, they are primarily polyclonal, containing many types of antibodies in lesser quantities. Hyperimmune globulins are used for postexposure prophylaxis for several diseases, including hepatitis B, rabies, tetanus, and varicella.

Heterologous hyperimmune serum, also known as antitoxin, is produced in animals, usually horses, and contains antibodies against only one antigen. In the United States, antitoxins are available for the treatment of botulism and diphtheria. These products can cause serum sickness, an immune reaction to the horse protein.

Immune globulin products from human sources are primarily polyclonal; they contain many kinds of antibodies. Monoclonal antibody products have many applications, including the diagnosis of certain types of cancer (colorectal, prostate, ovarian, breast), treatment of cancer (B-cell chronic lymphocytic leukemia, non-Hodgkin lymphoma), prevention of transplant rejection, and treatment of autoimmune (Crohn's disease, rheumatoid arthritis) and infectious diseases.

While certain antibody products, such as immune globulins, interfere with the immune response to live-virus vaccines, monoclonal antibody products do not because they are directed against one antigen or a closely related group of antigens. A monoclonal antibody product, palivizumab (Synagis), is available for the prevention of respiratory syncytial virus (RSV) infection. Since Synagis only contains RSV antibody, it will not interfere with the response to a live vaccine.

Active Immunity

Active immunity is protection produced by a person's own immune system. The immune system is stimulated by an antigen to produce antibody-mediated and cell-mediated immunity. Unlike passive immunity, which is temporary, active immunity usually lasts for many years, often for a lifetime.

One way to acquire active immunity is to survive infection with the disease-causing form of the organism. In general, once persons recover from infectious diseases, they will have lifelong immunity to that disease (there are exceptions, e.g., malaria). 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 memory B-cells continue to circulate in the blood and reside in the bone marrow for many years. Upon re-exposure to the antigen, these memory

NOTES

NOTES

cells begin to replicate and produce antibody rapidly to reestablish protection.

Another way to produce active immunity is by vaccination. Vaccines contain antigens that stimulate the immune system to produce an immune response that is often similar to that produced by the natural infection. With vaccination, however, the recipient is not subjected to the disease and its potential complications.

Many factors may influence the immune response to vaccination. These include the presence of maternal antibody, the nature and dose of antigen, the route of administration, and the presence of an adjuvant (e.g., aluminum-containing material added to improve immunogenicity of the vaccine). Host factors, such as age, nutrition, genetics, and coexisting disease, may also affect the immune response. The more similar a vaccine is to the disease-causing form of the organism, the better the immune response to the vaccine.

Classification of Vaccines

There are two basic types of vaccines. Their characteristics are different and determine how each type is used.

1. Live, attenuated, and
2. Inactivated.

Live, Attenuated Vaccines

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

To produce an immune response, live, attenuated vaccines must replicate in the vaccinated person. A relatively small dose of administered virus or bacteria replicates in the body and creates enough of the organism to stimulate an immune response.

Although live, attenuated vaccines replicate, they usually do not cause disease such as that caused by the wild form of the organism. When a live, attenuated vaccine does cause disease, it is usually much milder than the natural disease and is considered an adverse reaction to the vaccine.

The immune response to a live, attenuated vaccine is virtually identical to that produced by a natural infection because the immune system does not differentiate between an infection with a weakened vaccine virus and an infection with a wild

virus. Injected live, attenuated vaccines produce immunity in most recipients with one dose. However, a small percentage of recipients do not respond to the first dose of an injected live, attenuated vaccine (such as measles, mumps, and rubella [MMR]) and a second dose is recommended to provide an extremely high level of immunity in the population. Orally administered live, attenuated vaccines require more than one dose to produce immunity.

A live, attenuated vaccine may cause severe or fatal infections as a result of uncontrolled replication of the vaccine virus or bacteria. However, this only occurs in persons with a weakened immune system (e.g., from leukemia, treatment with certain drugs, or human immunodeficiency virus [HIV] infection).

A live, attenuated vaccine virus could theoretically revert to its original pathogenic form. This is known to happen only with live (oral) polio vaccine, which is no longer available in the United States.

Active immunity from a live, attenuated vaccine may not develop because of interference with the vaccine virus by circulating antibody. Antibody from any source (e.g., transplacental transfer to infants, transfusion of blood products) can interfere with replication of the vaccine organism and lead to poor response or no response to the vaccine (also known as vaccine failure).

Live, attenuated vaccines are fragile and can be damaged or destroyed by heat and light. They must be stored and handled carefully. The live, attenuated viral vaccines currently available and routinely recommended in the United States are MMR, varicella, rotavirus, and influenza (intranasal). Other non-routinely recommended live vaccines include adenovirus vaccine (used by the military), typhoid vaccine (Ty21a), and Bacille Calmette-Guerin (BCG). BCG is not used as a vaccine in the United States, but as a treatment for bladder cancer.

Inactivated Vaccines

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

The immunity provided by inactivated vaccines is generally not as long-lasting as that obtained from live, attenuated vaccines. Multiple doses over time are needed to obtain ongoing immunity. In general, the first dose does not produce protective immunity, but "primes" the immune system. A protective

NOTES

NOTES

immune response develops after the second or third dose. Unlike live vaccines, which produce an immune response that closely resembles natural infection, the immune response to an inactivated vaccine is mostly antibody production. Little or no cellular immunity results. Antibody titers against inactivated antigens diminish with time. As a result, some inactivated vaccines may require periodic supplemental doses to increase, or "boost," antibody titers.

Inactivated vaccines include whole-cell inactivated vaccines (e.g., polio, hepatitis A, and rabies vaccines), subunit vaccines (e.g., influenza and pneumococcal vaccines), toxoids (e.g., diphtheria and tetanus toxoid), and recombinant vaccines (e.g., hepatitis B, human papillomavirus [HPV], and influenza [Flublok brand]).

Whole-cell inactivated vaccines contain bacteria or viruses that have been killed through a physical or chemical process. Whole-cell inactivated viral vaccines against polio, hepatitis A, and rabies are available in the United States. A vaccine made from whole killed pertussis (whooping cough) bacteria is available outside the United States.

Subunit vaccines contain a portion of the bacteria or virus. The portion of the organism selected is the part needed to produce a protective immune response. Antigens in subunit vaccines can be protein, polysaccharide, or a combination of polysaccharide and protein molecule (i.e., conjugate vaccine).

Conjugate subunit vaccines (e.g., *Haemophilus influenzae* type b and pneumococcal conjugate vaccines) are produced by chemically attaching a polysaccharide from the surface of bacteria to a protein molecule through a process called conjugation. Conjugating a polysaccharide antigen to a protein molecule produces long-lasting protective immunity to the polysaccharide antigen.

The immune response to a pure polysaccharide vaccine is typically T-cell-independent, which means these vaccines can stimulate B-cells without the assistance of T-helper cells. T-cell-independent antigens, including polysaccharide vaccines, are not consistently immunogenic in children younger than age 2 years, probably because of immaturity of the immune system. Attaching the polysaccharide antigen to a protein makes it possible to prevent bacterial infections in populations where a polysaccharide vaccine is not effective or provides only temporary protection.

Toxoid vaccines are made using inactivated toxins produced by bacteria. These protein-based toxins are inactivated using heat, chemicals, or other methods. Some bacteria (e.g., tetanus, diphtheria) cause disease by producing toxins. The ability of the immune system to recognize and eliminate these toxins provides protection from the disease.

Recombinant vaccines are produced by recombinant DNA technology. Recombinant DNA technology enables the combination of DNA from two or more sources. Hepatitis B, human papillomavirus (HPV), and influenza (Flublok brand) vaccines are produced by insertion of a segment of the respective viral gene into the gene of a yeast cell or virus. The modified yeast cell or virus produces pure hepatitis B surface antigen, HPV capsid protein, or influenza hemagglutinin when it grows. Serogroup B meningococcal vaccines are proteins and outer membrane vesicles generated by recombinant technology.

Acknowledgements

The editors would like to acknowledge Jennifer Hamborsky, Andrew Kroger, Ginger Redmon, and Skip Wolfe for their contributions to this chapter.

Selected References

American Academy of Pediatrics. Active and passive immunization. In: Kimberlin D, Brady M, Jackson M, et al., eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics;2018:13–64.

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

Plotkin S. Vaccines, vaccination, and vaccinology. *J Infect Dis* 2003;187:1347–59.

Siegrist C. Vaccine immunology. In: Plotkin S, Orenstein W, Offit P, et al., eds. Plotkin's *Vaccines.* 7th ed. Elsevier;2018:16–34.

NOTES

NOTES

Elaine Miller, RN, BSN, MPH and A. Patricia Wodi, MD

This chapter discusses best practices related to vaccine timing and spacing, dosing, adverse reactions, and contraindications and precautions for routinely recommended vaccines in the United States. A more thorough discussion of issues common to the use of multiple vaccines and non-routinely recommended vaccines (e.g., rabies, smallpox) can be found in the *General Best Practice Guidelines for Immunization: Best Practices Guidance of the Advisory Committee on Immunization Practices*. Information about recommended travel vaccines (e.g., yellow fever, typhoid) can be found in CDC's *Yellow Book*.

Timing and Spacing of Vaccines

Timing and spacing of vaccine doses are two of the most important considerations for the appropriate use of vaccines. Specific circumstances commonly encountered in immunization practice are the intervals between doses of the same vaccine, simultaneous and nonsimultaneous administration of different vaccines, and the intervals between antibody-containing blood products and live attenuated vaccines (particularly measles- and varicella-containing vaccines).

Interval Between Doses of the Same Vaccine

Most vaccines in the immunization schedule require two or more doses for development of an adequate and persistent antibody response. Vaccinations are recommended beginning with the youngest age group at risk for a disease for whom vaccine efficacy and safety have been demonstrated. Studies have demonstrated that following the recommended ages and intervals between doses of the same antigen(s) provides optimal protection. As a general rule, decreasing the interval between doses in a multiple-dose vaccine series may interfere with antibody response and protection.

For routine vaccination, vaccine doses should not be administered earlier than the minimum ages or at less than the minimum intervals. However, exceptions may occasionally be necessary. One exception involves administering a dose up to 4 days before the minimum age or interval to avoid missing an opportunity to vaccinate. The patient may have come to the office early or for an appointment not specifically for vaccination. In these situations, the provider can consider administering the vaccine earlier than the minimum age or interval. However, if the provider has confidence that the patient will return for a later visit, it is preferable to reschedule vaccination on or after the recommended minimum age or interval. If the patient is new to the provider or habitually misses appointments, it may be preferable to administer the vaccine early. These early doses administered within 4 days of

NOTES

NOTES

the minimum age or interval are considered valid. In certain situations, state or local requirements might mandate doses of selected vaccines be administered on or after specific ages, superseding this 4-day grace period. Doses administered 5 days or more before the minimum age or interval should not be counted as valid and should be repeated as age-appropriate.

Other exceptions are administering doses in a vaccine series at shorter intervals than recommended when a person 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. An example is an infant age 6 through 11 months receiving 1 dose of MMR vaccine prior to international travel (not to be considered valid as part of the routinely recommended series) or administering the second dose of measles vaccine before age 4 years during a measles outbreak (considered valid as long as a minimum interval of at least 4 weeks from the prior dose was heeded and the child was age 12 months or older).

In some cases, a scheduled dose of vaccine may be administered late. A late dose should be administered at the next visit. Available data indicate intervals between doses that are longer than those routinely recommended do not affect seroconversion rates or titers when the schedule is completed. Therefore, it is not necessary to restart a series or add doses of any vaccine because of an extended interval between doses.

Simultaneous and Nonsimultaneous Vaccine Administration

Simultaneous Administration of Different Vaccines

Simultaneous administration (i.e., administration of two or more vaccines on the same day) of all recommended vaccines is important because it increases the probability that an individual will be fully vaccinated at the appropriate age. It is also an important part of immunization practice when a health care provider is uncertain that a patient will return for additional doses of vaccine.

As a general rule, almost all vaccines can be administered at the same visit. Exceptions to this include:

- PCV13 (Prevnar 13) vaccine and MenACWY-D (Menactra) vaccine should not be administered simultaneously to persons with functional or anatomic asplenia or HIV. Menactra brand meningococcal conjugate vaccine is thought to interfere with the antibody response to Prevnar 13. When both Prevnar 13 and Menactra are indicated, Prevnar 13 should be administered first, followed by Menactra at least 4 weeks later.

- PCV13 (Prevnar 13) vaccine and PPSV23 (Pneumovax 23) vaccine should not be administered at the same visit; studies show a better immune response when Prevnar 13 is administered before Pneumovax 23. When both Prevnar 13 and Pneumovax 23 are indicated, Prevnar 13 should be administered first, and Pneumovax 23 should be administered either at least 8 weeks later or at least 1 year later, depending on the age and health conditions of the vaccine recipient.
- Varicella (VAR [Varivax]) vaccine should not be administered simultaneously with smallpox vaccine.

Combination vaccines are generally preferred over simultaneous administration of single-component vaccines. Combination vaccines contain components that can be divided into independently available routine vaccines and can reduce the number of injections needed. Considerations for using combination vaccines should include an assessment of the number of injections, availability of vaccine, likelihood of improved vaccination coverage, likelihood of patient return, and issues regarding storage and cost. Considerations should also include patient choice and the potential for adverse events.

There is an increased risk of febrile seizures following the first dose of the combination measles, mumps, rubella, varicella (MMRV [ProQuad]) vaccine compared with separate administration of MMR vaccine (MMR-II) and VAR vaccine (Varivax). For the first dose, MMR and varicella vaccines should be administered separately for children age 12 through 47 months unless the parent or caregiver expresses a preference for MMRV vaccine.

Nonsimultaneous Administration of Live Vaccines

If any combination of live, injected vaccines (MMR-II, ProQuad, Varivax) or live, attenuated influenza vaccine (LAIV [FluMist]) is not administered simultaneously, the vaccine doses should be separated by at least 4 weeks. This interval is intended to reduce or eliminate interference from the vaccine administered first with the vaccine administered later. If any two of these vaccines are administered at an interval of less than 4 weeks, then the vaccine administered second should be repeated in 4 weeks or serologic testing should be performed following MMR-II and ProQuad to confirm their effectiveness (serologic testing is not recommended following FluMist or Varivax vaccines).

Live vaccines administered by the oral route (e.g., typhoid TY21a, [Vivotif], rotavirus, and adenovirus vaccines) are not believed to interfere with parenteral or intranasal live vaccines or with each other. Therefore, they may be administered simultaneously with or at any time before or after other live vaccines.

NOTES

NOTES

Vaccines and Antibody-Containing Products

Antibody, in the form of immune globulin, might be administered simultaneously with or around the same time as certain vaccines; for example, as postexposure prophylaxis for certain diseases, such as hepatitis B, rabies, and tetanus. Immune response to some live attenuated vaccines can be affected by receipt of immune globulin, depending on the type of vaccine, amount of antibody, and timing of administration. Immune response to inactivated vaccines are generally not affected by antibody-containing products. Inactivated vaccines can be administered before, after, or at the same time as the antibody products. However, the presence of circulating antibody to a vaccine antigen might reduce or eliminate the immune response to that vaccine. The vaccine antigen should be administered at a site distant from where the immune globulin was injected.

Live, Attenuated Injectable Vaccines

Live, attenuated vaccines must replicate to produce an immune response. Antibody against injected live vaccine antigen may interfere with replication. If measles, mumps, and rubella (MMR [MMR-II]), varicella (VAR [Varivax]), or combination measles, mumps, rubella, and varicella (MMRV [ProQuad]) vaccines must be administered around the same time as antibody, the two must be separated by enough time to prevent the antibody from interfering with viral replication. If these live vaccines are administered first, it is necessary to wait at least 2 weeks before administering the antibody. If the interval between the vaccine and antibody is less than 2 weeks, the recipient should be tested for immunity or the vaccine dose should be repeated. If the antibody is administered first, it is necessary to wait until the antibody has waned before administering the vaccine. This will reduce the chance of interference by the antibody.

An exception to the waiting period for antibody to wane before vaccination is the low dose of RhoGam or Rhophylac (anti-Rho(D) globulin) or any other blood product administered to women who do not have evidence of immunity to rubella or varicella during the last trimester of pregnancy or at delivery. Although passively acquired antibodies can interfere with the response to rubella vaccine, the low dose of anti-Rho(D) globulin has not been demonstrated to reduce the response to the rubella vaccine. These women should receive MMR-II, Varivax, or ProQuad as indicated immediately after delivery and, if possible, be tested 3 or more months later to ensure immunity to rubella and, if necessary, to measles.

Some blood products contain negligible antibody or type-specific antibody which do not interfere with vaccine replication. These products can be administered at any time

before or after administration of MMR or varicella-containing vaccines. Palivizumab (Synagis), used to prevent respiratory syncytial virus (RSV) infection in some infants and young children, contains antibody directed only at RSV. Washed red blood cells contain a negligible amount of antibody.

Live, Attenuated Oral and Intranasal Vaccines

Rotavirus vaccines (RV1 [Rotarix] and RV5 [RotaTeq]) and LAIV (FluMist) are not known to be affected by the administration of immune globulin or blood products. They may be administered simultaneously with blood products or separated from them by any interval.

Doses

Many factors influence the number of doses recommended in a vaccine series, including the type of vaccine, epidemiology of the disease, and host factors (e.g., age, presence of underlying diseases). For live, injected vaccines, the first dose administered at the recommended age usually provides protection. An additional dose is administered to provide another opportunity for vaccine response in the small proportion of recipients who do not respond to the first dose. For instance, approximately 95% of recipients respond to a single dose of measles vaccine. The second dose is administered to ensure that nearly 100% of persons are immune. Immunity following live vaccines is long-lasting, and booster doses are usually not necessary.

For inactivated vaccines, the first dose administered at the recommended age usually does not provide protection (hepatitis A vaccine is an exception). A protective immune response may not develop until after dose 2 or 3. For inactivated vaccines, antibody titers may decrease below protective levels after a few years. This phenomenon is most notable with pertussis vaccine. Tetanus and diphtheria vaccine-induced immunity also wanes. For these vaccines, a booster dose is administered to raise antibody back to protective levels.

Not all inactivated vaccines require boosting throughout the lifetime. For example, additional doses of *Haemophilus influenzae* type b vaccine are not required after completion of the infant primary series and booster dose because *H. influenzae* type b disease is rare in persons older than age 5 years. Hepatitis B vaccine does not require boosting in immunocompetent persons because of immunologic memory of the vaccine and the long incubation period for hepatitis B. Immunologic memory produces an "autoboost," which means exposure to the virus causes the established immune memory to respond faster than the virus can cause disease.

NOTES

NOTES

Adverse Reactions Following Vaccination

An adverse reaction or side effect is an untoward effect caused by a vaccine. An adverse reaction is different from a vaccine adverse event. Vaccine adverse event refers to any medical event that occurs following vaccination. An adverse event could be a true adverse reaction or a coincidental event, with further investigation needed to distinguish between them. Health care providers are required by law to report certain adverse events after vaccination. Details on reporting adverse events after vaccination can be found at https://vaers.hhs.gov/

Allergic reactions may be caused by the vaccine antigen itself or some other vaccine component, such as cell culture material or a stabilizer, preservative, or antibiotic used to inhibit bacterial growth. Severe allergic reactions (e.g., anaphylaxis) may be life-threatening but fortunately are rare. The risk of an allergic reaction can be decreased by effective screening prior to vaccination. All providers who administer vaccines must have an emergency protocol, supplies, and training to treat anaphylaxis.

Local adverse reactions (e.g., pain, swelling, and redness at the injection site) are the most common adverse reactions following vaccination. They generally occur within a few hours of the injection and are usually mild and self-limited. Local reactions may occur with up to 80% of vaccine doses, depending on the type of vaccine. On rare occasions, local reactions may be severe. These reactions, referred to as Arthus reactions, are most frequently seen with diphtheria and tetanus toxoids. Arthus reactions are not allergic reactions. They are believed to be due to high titers of antibody, usually caused by too many doses of toxoid.

Systemic adverse reactions (e.g., fever, myalgia, rash, headache) may occur following vaccination. Adverse reactions such as fever or rash following live, attenuated vaccines may be similar to a mild form of the natural disease, with symptoms produced from viral replication. Systemic adverse reactions are usually mild and occur 3 through 21 days after the vaccine was administered. Systemic adverse reactions from live attenuated vaccines are seen at longer intervals following vaccine administration because they are caused by replication of vaccine virus in the body, which occurs over several days. FluMist may cause upper respiratory symptoms rather than influenza-like symptoms since it replicates in the mucous membranes of the nose and throat and not in the lungs. Systemic adverse reactions were relatively frequent with diphtheria-tetanus-whole-cell-pertussis (DTP) vaccine, which contained a whole-cell pertussis component. Systemic adverse events are less common with acellular pertussis vaccine.

Contraindications and Precautions to Vaccination

Contraindications and precautions to vaccination generally dictate circumstances when vaccines should not be administered. Some contraindications and precautions are temporary, and the vaccine can be administered later.

Contraindications

A contraindication is a health condition in the recipient that increases the likelihood of a serious adverse reaction to a vaccine. For instance, administering MMR-II vaccine to a person with a true anaphylactic allergy to gelatin could cause serious illness or death in the recipient. In general, vaccines should not be administered when a contraindication is present.

Medical conditions that are contraindications to vaccination include:

- A severe allergic reaction (e.g., anaphylaxis) to a vaccine component is a contraindication to any vaccine containing that component, and a severe allergy following a dose of vaccine is a contraindication to subsequent doses of that vaccine.
- Severe immunosuppression is a contraindication to live, attenuated vaccines.
- A history of intussusception is a contraindication to rotavirus vaccination.
- Encephalopathy not due to another identifiable cause and occurring within 7 days of pertussis vaccination is a contraindication to subsequent doses of pertussis-containing vaccine.

Use of aerosolized steroids, such as inhalers for asthma, is not a contraindication to vaccination; nor are alternate-day, rapidly tapering, and short (less than 14 days) high-dose schedules, topical formulations, and physiologic replacement steroid dose schedules.

Precautions

A precaution is a health condition in the recipient that might increase the chance or severity of a serious adverse reaction, might compromise the ability of the vaccine to produce immunity (such as administering measles vaccine to a person with passive immunity to measles from a blood transfusion), or might cause diagnostic confusion. Injury could result, but the chance of this happening is less than with a contraindication. In general, vaccines should be deferred when a precaution is

NOTES

NOTES

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 administer the vaccine.

Medical conditions that are precautions to vaccination include:

- Moderate or severe acute illness, with or without fever, is a precaution for all vaccines.
- Guillain-Barré syndrome (GBS) occurring 6 weeks or less after a previous dose of a tetanus toxoid-containing vaccine is a precaution for tetanus toxoid-containing vaccines.
- GBS occurring 6 weeks or less after a previous dose of influenza vaccine is a precaution for influenza vaccines.
- History of thrombocytopenia or thrombocytopenic purpura is a precaution for MMR vaccine.
- Chronic gastrointestinal disease, or altered immunocompetence other than SCID are precautions for rotavirus vaccine. Spina bifida or bladder exstrophy are precautions for Rotarix (RV1) but not for RotaTeq RV5 vaccine.
- Recent receipt of antibody-containing blood products is a precaution for MMR- and varicella-containing vaccines.
- History of Arthus-type hypersensitivity reaction after a previous dose of diphtheria toxoid or tetanus toxoid vaccine is a precaution to these vaccines; vaccination should be deferred until at least 10 years have elapsed since the last tetanus-toxoid-containing vaccine.
- Progressive neurologic disorder, including infantile spasms, uncontrolled epilepsy, or progressive encephalopathy is a precaution for DTaP and Tdap vaccination; individual clinical decision-making should be used to guide revaccination until neurologic status has been clarified and stabilized.

Family History of Adverse Events

With few exceptions, family medical history is not a contraindication or precaution to vaccines. A family history of immunosuppression in first-degree relatives (i.e., parents or siblings) is a contraindication to MMR and varicella-containing vaccines unless the potential vaccine recipient's immunocompetence has been verified either clinically or by a laboratory. A family history of seizures is a precaution for MMRV vaccination.

Contraindications and Precautions in Persons with Specific Health Conditions

Persons with a History of Allergic Reactions

A severe allergic reaction (e.g., anaphylaxis) following a dose of vaccine is a contraindication for a subsequent dose of that vaccine. Anaphylactic reactions are mediated by IgE, occur within minutes or hours of receiving the vaccine, and require emergency medical attention. Anaphylaxis involves two or more organ systems (dermatologic, cardiovascular, respiratory, and/or gastrointestinal) simultaneously. Symptoms and signs of anaphylactic reactions include generalized urticaria (hives), swelling of the mouth and throat, difficulty breathing, wheezing, hypotension, or shock. Anaphylaxis after vaccination occurs rarely and can often be prevented by appropriate screening.

Persons may be allergic to a vaccine antigen or to a vaccine component such as an animal protein, antibiotic, preservative, or stabilizer. The most common animal protein allergen is egg protein found in influenza vaccines prepared using embryonated chicken eggs. Asking persons whether they can eat eggs without adverse effects is a reasonable way to screen for those who might be at risk if they receive egg-containing influenza vaccines. Persons with a history of egg allergy who have experienced only hives after exposure to egg should receive influenza vaccine. Influenza vaccine may also be administered to persons who report having had reactions to egg involving symptoms other than hives (such as swelling of the throat and mouth, difficulty breathing, lightheadedness, or recurrent emesis) or who required epinephrine or another emergency medical intervention. If egg-containing influenza vaccine is administered to persons who report having had reactions to egg involving symptoms other than hives, it should be administered in an inpatient or outpatient medical setting and supervised by a health care provider able to recognize and manage severe allergic conditions. A previous severe allergic reaction to influenza vaccine, regardless of the component suspected of being responsible for the reaction, is a contraindication to future receipt of the vaccine.

Studies show that children who have a history of severe allergy to eggs rarely have reactions to MMR-II and ProQuad vaccine. This is probably because measles and mumps vaccine viruses are both grown in chick embryo fibroblasts, not actually in eggs. It appears gelatin, not egg, might be the cause of allergic reactions to MMR-II. Children with egg allergies may be vaccinated with MMR-II or ProQuad without prior skin testing.

Certain vaccines contain trace amounts of neomycin. Persons who have experienced an anaphylactic reaction to neomycin should not receive these vaccines. Most often, neomycin allergy

NOTES

NOTES

presents as contact dermatitis, a manifestation of a delayed-type (cell-mediated) immune response, rather than anaphylaxis. A history of delayed-type reactions is not a contraindication for administration of neomycin-containing vaccines.

Latex, which is sap from the commercial rubber tree, contains naturally occurring impurities (e.g., plant proteins and peptides), which are believed to be responsible for allergic reactions. The most common type of latex sensitivity is contact-type (type 4) allergy, usually resulting from prolonged contact with latex-containing gloves. Among patients with diabetes, latex allergies associated with injection procedures have been described. Latex-related allergic reactions after vaccination are rare. If a person reports a severe allergic reaction to latex, vaccines supplied in vials or syringes containing 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 containing latex can be administered.

Pregnancy

Inactivated influenza and Tdap vaccines are recommended during pregnancy.

Live, attenuated viral vaccines (e.g., MMR-II, Varivax, FluMist) are contraindicated during pregnancy because of the theoretical risk of virus transmission to the fetus. Sexually active women who receive MMR-II or Varivax should be instructed to practice careful contraception for 1 month following receipt of either vaccine. On theoretical grounds, inactivated poliovirus (IPV) vaccine should not be administered during pregnancy; however, it may be administered if the risk of exposure (e.g., during travel to endemic disease areas) is imminent and immediate protection is needed. HPV vaccine should not be administered to pregnant women. There is no recommendation to administer *H. influenzae* type b vaccine (ActHIB, Hiberix, PedvaxHIB), pneumococcal conjugate vaccine (Prevnar 13), or serogroup B meningococcal vaccine (Bexsero, Trumenba) to a pregnant woman. Hepatitis A vaccine (Havrix, Vaqta), hepatitis B vaccine (Engerix-B, Recombivax HB), and meningococcal conjugate vaccine (Menactra, Menveo) can be administered to a pregnant woman in some circumstances. Data on use of HepB-CpG (Heplisav-B), MenACWY-TT (MenQuadfi), and the pneumococcal polysaccharide (PPSV23 [Pneumovax 23]) vaccines during pregnancy are limited. For more detailed information about vaccinations during pregnancy see https://www.cdc.gov/vaccines/pregnancy/hcp-toolkit/guidelines.html

Immunosuppression

Live, attenuated vaccines can cause severe or fatal reactions in immunosuppressed persons due to uncontrolled replication of the vaccine virus. Live vaccines should usually not be administered to severely immunosuppressed persons with congenital immunodeficiency, leukemia, lymphoma, or generalized malignancy. However, persons with isolated B-cell deficiency may receive varicella vaccine. Generally, the provider treating an immunosuppressed patient should determine the severity of that patient's immunosuppression.

Certain drugs can also cause immunosuppression. For instance, persons receiving cancer treatment with alkylating agents, antimetabolites, or radiation therapy should not receive live vaccines. Live vaccines can be administered after chemotherapy or radiation therapy has been discontinued for at least 3 months. In addition, persons receiving large doses of corticosteroids should not receive live vaccines. This includes persons receiving 20 milligrams or more of prednisone daily or 2 milligrams or more of prednisone per kilogram of body weight per day for 14 days or longer.

The safety and efficacy of live, attenuated vaccines administered concurrently with recombinant human immune mediators and immune modulators are not known. There is evidence that use of therapeutic monoclonal antibodies, especially the anti-tumor necrosis factor (TNF) agents (e.g., adalimumab, infliximab, etanercept, golimumab, and certolizumab pegol), may lead to reactivation of latent tuberculosis infection and disease. These agents might also predispose persons to other opportunistic infections. Because these drugs vary dramatically in the scope and number of immune-system-targeted components, it is prudent to avoid administering live, attenuated vaccines while patients are taking these drugs. For vaccination against seasonal influenza, inactivated injectable alternatives are available.

The time health care providers should wait to administer a live-virus vaccine after immune modulator drugs have been discontinued is not specified by the Advisory Committee on Immunization Practices (ACIP) or other authoritative guidelines. No basis exists for interpreting laboratory studies of immune parameters with vaccines' safety or efficacy. Lymphocyte-depleting agents such as alemtuzumab and rituximab may cause prolonged immunosuppression. Both inactivated and live vaccines should be withheld at least 6 months following therapy with anti-B cell antibodies. Some experts recommend longer than 6 months following anti-B cell antibodies. The optimal time for restarting immunosuppressive therapy after vaccination with live vaccines has not been studied, but the Infectious Diseases Society of America (IDSA) recommends waiting at least 1 month.

NOTES

NOTES

Consultation with the prescribing physician (and possibly a hospital pharmacist) is recommended for management of individual patients and guidance in estimating a patient's degree of immunosuppression. Inactivated vaccines cannot replicate, so they are safe to use in immunosuppressed persons. Certain vaccines are recommended or specifically encouraged because immunosuppression is a risk factor for complications from certain vaccine-preventable diseases (i.e., influenza, invasive pneumococcal disease, invasive meningococcal disease, invasive *H. influenzae* type b disease, and hepatitis B). However, because a relatively functional immune system is required to develop an immune response to a vaccine, the immune response may be poor, depending on the degree of immunosuppression present.

HIV Infection

Persons infected with human immunodeficiency virus (HIV) may not manifest disease, or they may be severely immunosuppressed. In general, the same vaccination recommendations apply as for other types of immunosuppression. Live-virus vaccines are usually contraindicated in those with severe immunosuppression, but inactivated vaccines may be administered if indicated.

For persons infected with HIV:

- Varivax can be considered for persons who are not severely immunocompromised, since varicella infection can be severe for HIV-positive persons and is often associated with complications.
- MMR-II vaccine should be administered to persons who are not severely immunocompromised.
- FluMist should not be administered, but age-appropriate inactivated or recombinant influenza vaccine should be administered.

Hematopoietic Cell Transplant Recipients

Hematopoietic cell transplant (HCT) results in immunosuppression due to ablative therapy administered before the transplant and therapies to prevent or treat graft-versus-host disease. In addition, HCT recipients are at increased risk for vaccine-preventable diseases because antibody titers decline 1 to 4 years after HCT if the recipient is not revaccinated.

HCT recipients at increased risk should be routinely vaccinated after HCT against tetanus, poliovirus, measles, mumps, rubella, *Streptococcus pneumoniae*, and *H. influenzae* type b, regardless of the source of the transplanted cells. Specifically:

- MMR and varicella-containing vaccines should be administered 24 months after transplantation if the HCT recipient is presumed to be immunocompetent.

- Revaccination with inactivated vaccines, including influenza vaccine, should begin 6 months after HCT. However, influenza vaccine may be administered as early as 4 months after HCT, if needed.
- Three doses of Prevnar 13 should be administered 3-6 months after HCT, followed by a dose of PPSV23.
- A dose of MenACWY should also be administered 6 months after HCT.

Invalid Contraindications and Precautions to Vaccination

Sometimes certain conditions or circumstances are inappropriately considered to be contraindications or precautions to vaccination. Such conditions or circumstances are known as invalid contraindications and these misperceptions result in missed opportunities to administer needed vaccines. Some of the most common invalid contraindications are mild illnesses, pregnancy, breastfeeding, allergies that are not anaphylactic in nature, and certain aspects of the patient's family history.

Mild Illness

Children with a mild acute illness, such as a low-grade fever, an upper respiratory infection (URI), otitis media, or mild diarrhea, should be vaccinated on schedule.

Low-grade fever is not a contraindication to vaccination. Measuring temperature is not necessary before vaccination if the patient does not appear ill and does not report currently being ill. ACIP has not defined a body temperature above which vaccines should not be administered. The decision to vaccinate should be based on the overall evaluation of the person rather than an arbitrary body temperature.

Nonanaphylactic Allergy

If an allergy to a vaccine component is not severe (e.g., is not anaphylaxis), it is not a contraindication to that vaccine. Only a severe allergic reaction (e.g., anaphylaxis) to a vaccine component is a true contraindication to vaccination.

Allergy to Products Not Present in Vaccines

There is no contraindication or precaution for persons with nonspecific allergies, duck or feather allergies, or penicillin allergy, or for persons who have relatives with allergies or those taking allergy shots. Anyone with these allergies can and should be vaccinated. No vaccine available in the United States contains duck antigen or penicillin.

NOTES

NOTES

Antimicrobial Therapy

Antimicrobials do not influence the immune response to most vaccines. However, antiviral drugs may affect vaccine replication in some circumstances. FluMist should not be administered until 48 hours after cessation of oseltamivir and zanamivir, 5 days after cessation of peramivir, and 17 days after baloxavir. If possible, antiviral drugs (acyclovir, famciclovir) that are active against herpesviruses should be discontinued 24 hours before administration of a varicella-containing vaccine.

Breastfeeding

Breastfeeding does not decrease the response to any routinely recommended childhood vaccine and is not a contraindication to vaccination; however, breastfeeding is a precaution for yellow fever vaccine. Breastfeeding also does not extend or improve the passive immunity to vaccine-preventable disease that is provided by maternal antibody.

Household Contacts of Pregnant or Immunosuppressed Persons

Being a household contact of a pregnant woman or immunosuppressed person is usually not a contraindication to vaccination. In fact, it is critical that healthy household contacts of pregnant women and immunosuppressed persons be vaccinated. Vaccination of healthy contacts reduces the chance that pregnant women and immunosuppressed persons will be exposed to vaccine-preventable diseases.

Most routinely recommended vaccines, including live vaccines (MMR-II, Varivax, RotaTeq/Rotarix, and FluMist), can be administered to persons who are household contacts of pregnant or immunosuppressed persons. If a varicella vaccine recipient has a rash after vaccination, direct contact with susceptible household contacts with altered immunocompetence should be avoided until the rash resolves. All members of the household should wash their hands after changing the diaper of an infant who received rotavirus vaccine. This minimizes rotavirus transmission, as shedding may occur up to one month after the last dose. FluMist should not be administered to close contacts and caregivers of severely immunosuppressed persons who require a protected environment.

Preterm Birth

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

Studies demonstrate that decreased seroprotection rates might occur among infants with low birth weight (less than 2,000 grams) after administration of hepatitis B vaccine at birth.

However, by the chronological age of 1 month, all preterm infants, regardless of initial birth weight or gestational age, are likely to respond as adequately as older and larger infants.

Tuberculin Skin Test

Persons who need a tuberculin skin test (TST) can and should be vaccinated. All vaccines can be administered on the same day as a TST or at any time after a TST is administered. For most vaccines, there are no TST timing restrictions.

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

An interferon-gamma release assay (IGRA) tuberculosis test may be affected by live vaccines, so it is prudent to apply the same spacing rules as for TST and live vaccines.

Screening for Contraindications and Precautions to Vaccination

The key to preventing serious adverse reactions after vaccination is effective screening. Every patient should be screened for contraindications and precautions before administering any vaccine dose. Effective screening can be accomplished by asking a few questions:

Is the patient sick today?

There is no evidence that acute illness reduces vaccine efficacy or increases vaccine adverse events. However, as a precaution, if there is a moderate or severe acute illness, all vaccines should be deferred until the illness has improved. Mild illnesses (such as otitis media, URIs, and diarrhea) are *not* contraindications or precautions to vaccination and recommended vaccines should be administered on time.

Does the patient have allergies to medications, food, a vaccine component, or latex?

It may be more efficient to inquire about allergies in a generic way (i.e., allergies to any food or medication) rather than to inquire about allergies to specific vaccine components. Most persons will not be familiar with minor components of vaccines, but they should know if they or their child have had an allergic

NOTES

NOTES

reaction to a food or medication that was severe enough to require medical attention. If a person reports anaphylaxis after eating eggs, a specific protocol should be followed that includes determining the symptoms experienced. For information on egg allergies and influenza vaccination, please refer to the most recent ACIP influenza vaccination recommendations.

Has the patient experienced any reaction after receiving a vaccination?

A history of severe allergic reaction such as urticaria, wheezing or difficulty breathing, or circulatory collapse or shock (not fainting) following a previous dose of vaccine or to a vaccine component is a contraindication to further doses. A local adverse reaction (redness or swelling at the injection site) is not a contraindication to subsequent doses.

Some reactions after vaccination (e.g., Arthus reactions after a previous dose of diphtheria toxoid-containing or tetanus toxoid-containing vaccine) are considered as precautions to receiving further vaccine doses. ACIP recommends for persons with a history of Arthus-type hypersensitivity reactions after a previous dose of tetanus or diphtheria toxoid-containing vaccines should defer vaccination until at least 10 years have elapsed since the last tetanus toxoid-containing vaccine. Usually vaccines are deferred when a precaution is present. However, situations may arise when the benefit outweighs the risk (e.g., during a community pertussis outbreak).

Has the patient experienced a brain or other nervous system problem including seizures?

DTaP and Tdap are contraindicated for persons who have a history of encephalopathy not attributed to an identifiable cause within 7 days following DTaP, DTP, or Tdap vaccination. An unstable or progressive neurologic problem is a precaution for the use of DTaP and Tdap. Children with stable neurologic disorders (including seizures) unrelated to vaccination may be vaccinated as usual.

A history of GBS is a precaution for tetanus toxoid-containing and influenza vaccines, if it occurred within 6 weeks following a dose of the specific vaccine.

A personal or family history of febrile or afebrile seizures is a precaution for ProQuad vaccine. Simultaneous administration of MMR-II and Varivax is not associated with an increased risk of fever or seizures and is, therefore, preferred to ProQuad in children age 12 through 47 months.

Does the patient have a long-term health problem with heart, lung, kidney, or metabolic disease (e.g., diabetes), asthma, a blood disorder, no spleen, complement

component deficiency, a cochlear implant, or a CSF leak? Is the patient on long-term aspirin therapy?

These conditions are contraindications or precautions to LAIV. Age-appropriate inactivated or recombinant influenza vaccine is preferred for patients with these conditions.

Does the patient have cancer, leukemia, HIV/AIDS, or any other immune system problem?

Live virus vaccines (e.g., MMR-II, Varivax, MMRV, Rotarix and RotaTeq, and FluMist) are usually contraindicated in severely immunocompromised persons. However, there are exceptions. For example, MMR-II and Varivax are recommended for HIV-infected children who do not have evidence of severe immunosuppression.

Does the patient have a parent or sibling with an immune system problem?

MMR, VAR, and MMRV vaccines should not be given to a person with a family history of congenital or hereditary immunodeficiency in first-degree relatives (i.e., parents, siblings) unless the immune competence of the potential vaccine recipient has been clinically substantiated or verified by a laboratory.

Has the patient taken medications that affect the immune system, such as prednisone, other steroids, or anticancer drugs; drugs for the treatment of rheumatoid arthritis, Crohn's disease, or psoriasis; or has the patient had radiation treatment?

Live-virus vaccines (e.g., MMR-II, Varivax, FluMist) should be postponed until after chemotherapy or long-term, high-dose steroid therapy has ended.

Has the patient received a transfusion of blood or blood products, immune (gamma) globulin, or an antiviral drug in the past year?

Certain live-virus vaccines (i.e., MMR-II, ProQuad, and Varivax) may need to be deferred following administration of blood products, depending on the type of blood product and the interval since the blood product was administered.

Is the person pregnant or is there a chance she could become pregnant during the next month?

Live-virus vaccines (e.g., MMR-II, Varivax, FluMist) are contraindicated during pregnancy because of the theoretical risk of virus transmission to the fetus. Sexually active young women who receive MMR-II or Varivax should be instructed to practice careful contraception for 1 month following receipt of either vaccine. On theoretical grounds, inactivated poliovirus vaccine should not be administered during pregnancy; however,

NOTES

NOTES

it may be administered if the risk of exposure (e.g., during travel to endemic disease areas) is imminent and immediate protection is needed. HPV vaccine should not be administered to pregnant women. There is no recommendation to administer *H. influenzae* type b vaccine (ActHIB, Hiberix, PedvaxHIB), pneumococcal conjugate vaccine (Prevnar 13), or serogroup B meningococcal vaccine (Bexsero, Trumenba) to a pregnant woman. Hepatitis A vaccine (Havrix, Vaqta), hepatitis B vaccine (Engerix-B, Recombivax HB), and meningococcal conjugate vaccine (Menactra, Menveo), should be administered to pregnant women if routinely recommended or indicated. Data on use of HepB-CpG (Heplisav-B), MenACWY-TT (MenQuadfi), and the pneumococcal polysaccharide vaccine (Pneumovax 23) during pregnancy are limited.

Has the patient received vaccinations in the past 4 weeks?

A person who received either Flumist or a live, injectable vaccine (e.g., MMR-II, Varivax) in the past 4 weeks should wait 28 days before receiving another live vaccine. Inactivated vaccines may be administered at the same time or at any time before or after a live vaccine.

Has the patient (if the patient is a baby) ever had intussusception?

Intussusception is a contraindication for the rotavirus vaccine

Acknowledgements

The editors would like to acknowledge Maria Cano, Jennifer Hamborsky, Andrew Kroger, and Valerie Morelli for their contributions to this chapter.

Selected References

American Academy of Pediatrics. Active and passive immunization. In: Kimberlin D, Brady M, Jackson M, et al., eds. *Red Book: 2018 Report of the Committee on Infectious Diseases.* 31st ed. Itasca, IL: American Academy of Pediatrics;2018:13–64.

CDC. General Recommendations on Immunization: Recommendations of the Advisory Committee on Immunization Practices. *MMWR* 2011;60(No. RR-2):1–60.

Dietz V, Stevenson J, Zell E, et al. Potential impact on vaccination coverage levels by administering vaccines simultaneously and reducing dropout rates. *Arch Pediatr Adolesc Med* 1994;148(9):943–9.

Ezeanolue E, Harriman K, Hunter P, et al. *General Best Practice Guidelines for Immunization: Best Practices Guidance of the Advisory Committee on Immunization Practices (ACIP)*. www.cdc.gov/vaccines/hcp/acip-recs/general-recs/downloads/general-recs.pdf. Accessed December 27, 2019 and August 12, 2020.

Jackson B, Iqbal S, Mahon B. Updated recommendations for the use of typhoid vaccine—Advisory Committee on Immunization Practices, United States, 2015. *MMWR* 2015; 64(11):305–8.

James J, Burks A, Roberson P, et al. Safe administration of the measles vaccine to children allergic to eggs. *N Engl J Med* 1995;332:1262–6.

King G, Hadler S. Simultaneous administration of childhood vaccines: an important public health policy that is safe and efficacious. *Pediatr Infect Dis J* 1994;13(5):394–407.

Kroger A, Atkinson W, Pickering L. General immunization practices. In: Plotkin S, Orenstein W, Offit P, et al., eds. Plotkin's *Vaccines*. 7th ed. Elsevier;2018:96-120.

Rubin L, Levin M, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clin Infect Dis* 2014;58(3):e44–100.

NOTES

NOTES

Plotkin S. Vaccines, vaccination and vaccinology. *J. Infect Dis* 2003;187(9):1349–59.

Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplant recipients: a global perspective. *Biol Blood Marrow Transplant* 2009;15:1143–238.

Wood R, Berger M, Dreskin S, et al. An algorithm for treatment of patients with hypersensitivity reactions after vaccines. *Pediatrics* 2008;122(3):e771–7.

Immunization Strategies for Healthcare Practices and Providers

Adam Bjork, PhD and Valerie Morelli, BA

An important component of a vaccine provider's practice is ensuring vaccines reach all patients who need them, when they need them. Providers should implement systems and programs to provide effective vaccine delivery and to maintain and increase vaccination coverage in their practices. By creating a culture of immunization in the practice, both providers and patients can vaccinate with confidence.

Vaccine-preventable disease rates in the United States are at low levels. In 2018, four cases of rubella, one case of diphtheria, and 23 cases of tetanus were reported to CDC. However, the viruses and bacteria that cause vaccine-preventable diseases and death still exist. Diseases can be passed to unprotected persons or imported from other countries, as shown by the measles outbreaks that occurred in 2019 in New York and other states. Diseases such as measles, mumps, and pertussis can be more severe than often assumed, and can result in social and economic costs in addition to the physical costs: sick children miss school, parents have to take time off from work, and outbreaks can severely disrupt health care systems.

Sustainable systems for vaccinating children, adolescents, and adults must be continued in the context of a changing health care environment. High vaccination coverage cannot be maintained with one-time or short-term efforts. Greater understanding of strategies to increase and sustain vaccination coverage is necessary to create lasting, effective immunization delivery systems.

Many public health strategies have been used to increase vaccination coverage. Some, such as school entry laws, have been effective in increasing vaccination compliance, but the effectiveness of other strategies (e.g., advertising) is not well-documented. Some proven strategies (e.g., reducing costs, linking vaccination to Women, Infants, and Children [WIC] services, home visits) work well to increase coverage among specific populations, such as persons with limited access to immunization services. However, creating a culture of immunization within a health care practice also plays a critical role in maintaining and increasing vaccination coverage, as well as ensuring vaccines are delivered safely, effectively, and on time.

This chapter explores strategies health care providers can implement within their own practices. It covers system-level interventions such as quality improvement programs, as well as practice-level actions directed toward patients and provider staff.

NOTES

NOTES

Standards for Child, Adolescent, and Adult Immunization Practices

All health care providers in all settings are encouraged to ensure patients are up-to-date on vaccinations. The National Vaccine Advisory Committee's (NVAC) *Standards for Child and Adolescent Immunization Practices* and *Standards for Adult Immunization Practice* are recommended for use by all health care providers in the public and private sectors. The standards represent the most desirable immunization practices that providers should strive to achieve, regardless of whether they actually provide vaccinations. Providers implementing these standards will help ensure their patients are fully vaccinated, thereby helping to increase vaccination coverage and prevent outbreaks.

The *Standards for Child and Adolescent Immunization Practices* outline standards within five categories:

- Availability of vaccines
- Assessment of immunization status
- Effective communication about vaccine benefits and risks
- Proper storage and administration of vaccines and documentation of vaccinations
- Implementation of strategies to improve vaccination coverage

The *Standards for Adult Immunization Practice* include the following four standards:

- Assess immunization status of all adult patients at every clinical encounter
- Strongly recommend vaccines that patients need
- Administer vaccine or refer patients to a vaccine provider
- Document vaccines received by patients

The Guide to Community Preventive Services

The Community Preventive Services Task Force's *Guide to Community Preventive Services* is a collection of evidence-based findings based on effectiveness data and economic evidence. The vaccination section of the *Guide to Community Preventive Services* describes strong or sufficient evidence to support several provider-based immunization strategies discussed throughout this chapter.

Health Care Practice Quality Improvement Programs

Immunization quality improvement projects can be particularly effective because vaccination is a dynamic, critical, and measurable area of health care. It is rapidly evolving, making fast strides in some areas, but lagging in others, such as human papillomavirus (HPV) vaccination.

CDC encourages health care providers to consider implementing immunization quality improvement projects that:

1. Generate measurable increases in child, adolescent, and adult vaccination coverage.
2. Bring about measurable increases in HPV vaccination coverage, particularly rates of coadministration with other adolescent vaccines at age 11 or 12 years.
3. Bring about measurable increases in vaccination coverage of pregnant women, specifically for influenza and pertussis.
4. Reduce disparities in vaccination coverage, whether associated with race, ethnicity, type of health insurance (including lack of insurance), or any other factor resulting in less than optimal coverage.

Immunization Quality Improvement for Providers (IQIP)

CDC works with state, local, and territorial public health agencies to administer the Immunization Quality Improvement for Providers (IQIP) program to introduce and sustain new or improved immunization practices. Designed to increase on-time vaccination at the provider level, IQIP strategies are intended to increase vaccine uptake among child and adolescent patients in adherence with the Advisory Committee on Immunization Practices (ACIP) routine immunization schedule. IQIP is targeted toward quality improvement among providers enrolled in the Vaccines for Children (VFC) program.

IQIP Overview

IQIP serves to assist and support providers by identifying opportunities to improve vaccine uptake, determining options for improving immunization delivery practices, and ensuring providers are:

- Aware of and knowledgeable about vaccination coverage within their practices and missed opportunities to vaccinate
- Motivated to try new immunization service delivery strategies and incorporate changes into their practices
- Capable of sustaining changes and improvements to their immunization delivery services

NOTES

NOTES

The IQIP Process

IQIP is a 12-month process where public health representatives and VFC providers collaborate to identify strategies to increase vaccine uptake by improving and enhancing immunization workflow. The collaborative process includes vaccination coverage measurement at or near the time of an initial site visit and again one year later to evaluate progress. Technical assistance and support occur at two- and six-month intervals to aid providers in staying on course with implementing strategies to improve vaccine uptake.

IQIP strategies include:

- Scheduling the next immunization visit before the patient leaves the provider site
- Leveraging immunization information system (IIS) functionality to improve immunization practice
- Giving a strong vaccine recommendation for patients
- Optional strategies as defined by the needs of state and local communities

IQIP has replaced CDC's previous Assessment, Feedback, Incentives, and eXchange (AFIX) quality improvement program to better address the current health care environment.

Immunization Information Systems (IISs)

Many record-keeping tasks, as well as patient reminder and recall processes, can be greatly simplified by participation in an IIS. An IIS is a confidential, population-based, electronic database that records all vaccine doses administered by participating providers to persons residing within a given jurisdiction. In some areas, an IIS links to a complete medical record. While electronic health records (EHRs) include vaccination information, they may not provide a consolidated immunization history. An IIS provides a single data source for all community vaccination providers, enabling them to access records of persons receiving vaccinations from multiple providers. Data exchange between IISs, EHRs, and other information systems helps ensure timely vaccinations and records consolidation and allows immunization personnel to work more efficiently.

- At the point of clinical care, an IIS can provide consolidated immunization histories for use by a provider in determining appropriate patient vaccinations.
- At the population level, an IIS provides aggregate data on vaccinations for use in surveillance and program operations and for guiding public health action, with the goals of improving vaccination coverage and reducing rates of vaccine-preventable diseases.

The *Guide to Community Preventive Services* recommends IISs based on strong evidence that their use increases vaccination coverage. IISs can directly contribute to efforts to increase vaccination coverage through their abilities to:

- Create or support effective interventions such as patient reminder and recall systems, provider assessment and feedback, and provider reminders.
- Generate and evaluate public health responses to outbreaks of vaccine-preventable disease.
- Facilitate vaccine inventory management and accountability.
- Determine patient immunization status to inform decisions made by health care providers, clinicians, health departments, and schools.
- Aid surveillance and investigations of vaccination coverage, missed vaccination opportunities, and invalid dose administration.

Federal, state, and local public health agencies are continuing their efforts to improve IISs and to increase participation by vaccine providers. IISs are a key to increasing and maintaining vaccination coverage, and they offer advantages for providers, patients, and state and federal immunization program staff.

Essential Strategies for Health Care Practices

In addition to implementing a quality improvement program such as IQIP and participating in an IIS, other effective practice strategies exist that complement these programs. These strategies focus on patient confidence in vaccination and provider development of a culture of immunization within a practice.

Patient-Focused Strategies

Strong Vaccination Recommendation

A strong recommendation by a health care provider is a powerful motivator for patients to comply with vaccination recommendations. A recommendation from a health care provider remains the number one reason parents decide to vaccinate. Even initially reluctant adults are likely to receive an influenza vaccination when the health care provider's opinion of the vaccine is positive. Studies show a parent who receives a recommendation from their child's health care provider is four to five times more likely to get the HPV vaccine for their child.

Research has also shown the way a recommendation is presented makes a difference. When providers use a presumptive approach (one that assumes parents will choose to vaccinate), parents are more likely to accept vaccines than when a participatory approach (one that presents parents with

NOTES

NOTES

a decision to make) is used. A research study looking at health care provider's interactions with parents during vaccine visits showed parents were more likely to express concerns when providers used language asking parents about their vaccination plans. In this study, the presumptive approach resulted in significantly more parents accepting vaccines for their children, especially at first-time visits.

In practice, a provider using a presumptive approach might say, "Your child needs DTaP, Hib, and hepatitis B shots today." In contrast, a participatory approach might sound like, "Have you thought about the shots your child needs today?"

Take Time to Answer Questions

A strong recommendation will be enough to persuade many patients and parents to accept vaccines. However, some patients and parents might need more information or additional reassurance. An opportunity for questions should be provided before each vaccination. Discussion of the benefits and risks of vaccination is sound medical practice and providers are required by law to distribute vaccine information statements (VISs) before each dose of vaccine.

Surveys of parents of young children have shown while most parents plan to vaccinate on schedule, many parents still have questions, often related to vaccine ingredients, vaccine safety in general, or side effects. Data from CDC's National Immunization Survey (NIS)-Teen show when parents receive a recommendation for HPV vaccination from their child's health care provider, about a quarter of parents still choose not to have their child vaccinated. These parents may have concerns that need to be addressed about the safety or effectiveness of the vaccine.

If a parent has concerns, resists following the recommended immunization schedule, or questions a provider's strong recommendation, this does not necessarily mean they will not accept vaccines. Sometimes parents simply want to hear their provider's answers to their questions. Providers should be prepared to answer parents' questions succinctly and accurately, using terms parents understand. Effective, empathic vaccine risk communication is essential in responding to misinformation and concerns. It is important to remind parents that state laws for school or child care entry might require unvaccinated children to stay home from school during outbreaks. For patients who question or refuse vaccination, identifying common ground and discussing measures for deferring vaccination are more effective public health strategies than excluding these patients from a practice.

Providers can also train their staff in how to address basic vaccine questions to help save time during vaccine discussions and ensure parents hear consistent messages about vaccines.

For adults, providers can SHARE important information to help patients make informed decisions about vaccinations:

- ***Share*** the tailored reasons why the recommended vaccine is right for the patient based on his or her age, health status, lifestyle, occupation, or other risk factors.
- ***Highlight*** positive experiences with vaccines (personal or in the practice), as appropriate, to reinforce the benefits and strengthen confidence in vaccination.
- ***Address*** patient questions and concerns about the vaccine, including side effects, safety, and vaccine effectiveness in plain and understandable language.
- ***Remind*** patients that vaccines protect them and their loved ones from many common and serious diseases.
- ***Explain*** the potential costs of getting the disease, including serious health effects, time lost (missing work or family obligations), and financial costs.

When recommending influenza vaccine, it may also be helpful to explain that the vaccine can reduce the severity of illness among those who contract influenza.

Practice-Focused Strategies

Despite efforts by providers to adhere to appropriate immunization practices, there may be unknown obstacles to vaccination within the practice. Barriers to vaccination may be physical or psychological.

Physical barriers might include inconvenient clinic hours for working patients or parents, long waits at a clinic, or transportation issues. Providers are encouraged to determine the needs of their specific patient population and address obstacles to vaccination by taking appropriate actions, such as extending clinic hours or holding special vaccination events.

NOTES

NOTES

Psychological barriers to health care are often more subtle but may be just as important. Unpleasant experiences (e.g., fear of injections or difficulty leaving work for an appointment) may lead patients to postpone receiving needed vaccines. Concerns about vaccine safety contribute to some parents delaying or refusing recommended vaccines for their children. Overcoming such barriers calls for both knowledge and interpersonal skills on the part of the provider: knowledge of vaccines, recommendations, and reliable sources of accurate information to provide to patients and parents, as well as communication skills to address fears and misconceptions and provide a supportive and encouraging environment for patients.

System-Based Barriers

Missed Opportunities

Another obstacle to vaccination is a missed opportunity at a health care encounter in which a person is eligible to receive a vaccine but is not vaccinated completely. Missed opportunities can occur in all settings in which vaccines are offered, whether routine or not.

Missed opportunities occur for several reasons. Many health care providers avoid simultaneous administration of multiple injectable vaccines, frequently citing concerns about reduced immune response, adverse events, or perceived parental objections. These concerns are not supported by scientific data. Providers might even be unaware a child or adult needs a vaccination. In addition, providers sometimes follow invalid contraindications. A list of conditions incorrectly perceived as contraindications or precautions can be found in ACIP's *General Best Practice Guidelines for Immunization*.

Some reasons for missed opportunities relate to larger system issues, such as policies of only vaccinating children at well-care visits or not vaccinating siblings. Other reasons relate to institutional or bureaucratic regulations, such as state insurance laws denying reimbursement if a vaccine is administered during an acute-care visit. Several studies have shown eliminating missed opportunities could increase vaccination coverage by up to 20%.

Providers should implement systems to ensure the practice never misses an opportunity to vaccinate. Establish a policy to vaccinate at every visit, not just well visits, and schedule the next vaccination appointment before the patient leaves.

Adult Vaccination Barriers

Recognized barriers to adult vaccination include:

- Limited access to health care
- Multiple competing priorities for providers who care for adult patients
- Low awareness among adults about recommended vaccines and their benefits
- Challenges in coordinating care for adults who often have more than one medical provider
- A complicated adult immunization schedule
- Vaccine cost and reimbursement

Professional societies such as the American College of Physicians and American College of Obstetricians and Gynecologists have developed programs to support providers in improving vaccination coverage among their patients. These organizations and the National Adult and Influenza Immunization Summit offer educational resources, tools, and strategies to overcome challenges to vaccinating adults.

Creating a Culture of Immunization within a Practice

Creating a culture of immunization means including every member of the practice in vaccination efforts through:

- Consistent messaging about the importance of vaccines and about vaccine effectiveness and safety at all levels of the practice
- Adherence to proper vaccine storage, handling, and administration procedures
- Implementation of effective workflow processes to take advantage of every opportunity to vaccinate

Practices fostering support for vaccination:

- ***Save time.***

  Less time spent in vaccine conversations by involving practice staff in reinforcing vaccine recommendations and implementing effective workflow processes

- ***Save money.***

  Less money spent on lost vaccine by adhering to proper vaccine storage, handling, and administration practices

- ***Empower families.***

  Strengthened trust with families by helping patients and parents make informed decisions

NOTES

NOTES

Immunization Coordinator

It is an immunization delivery best practice for every provider setting to designate an immunization coordinator. This individual should be the provider site's point person for activities such as:

- Ensuring all vaccines are stored and handled correctly within the practice
- Helping to ensure all staff are trained in their role in immunization delivery and patient education
- Monitoring the practice's vaccination coverage
- Ensuring all staff know how to address questions from patients and parents so there is consistent messaging about vaccines
- Promoting and motivating staff implementation of immunization quality improvement strategies to improve immunization workflow, delivery, and, ultimately, vaccine uptake

By being familiar with the practice's vaccination coverage and understanding more about why some patients are not up-to-date with their vaccines, providers can implement interventions to increase coverage in their practice.

Vaccines for Children (VFC) Program

Cost can be a barrier to vaccination for many patients. In addition to evaluating the fee schedules for possible adjustments, providers should be knowledgeable about the VFC program, the state's Children's Health Insurance Program, and other vaccine-focused programs available within their jurisdiction.

A provider should consider participating in the VFC program if the practice sees children and adolescents (age 18 years or younger) who meet one or more of the following criteria:

- Medicaid-eligible
- Uninsured
- American Indian or Alaska Native
- Underinsured (only eligible to receive vaccines in a federally qualified health center or rural health clinic)

Being a VFC provider reduces up-front costs because practices are provided vaccines for VFC-eligible children at no cost. Providers can charge an administrative fee to offset the cost of doing business. VFC-eligible patients benefit because they avoid having to go somewhere else to get the vaccines they need.

Vaccination Reminders for Providers

Providers can create reminder systems to help them remember which vaccinations a patient needs. Examples of reminder systems are:

- A computer-generated list that notifies a provider which children being seen during the clinic session are past due on vaccinations
- A stamp with a message such as "no pneumococcal vaccine on record" that staff can put on the chart of a person age 65 years or older
- A "vaccination due" clip that staff attaches to the chart of an adolescent who has not had HPV vaccine
- An electronic reminder that appears when a provider accesses an electronic health record

Reminder systems vary according to the needs of the provider. In addition to raising vaccination coverage in the practice, systems serve to heighten staff awareness of the need to continuously check the vaccination status of their patients.

Standing Orders

Standing orders are protocols whereby nonphysician medical personnel may vaccinate patients without direct physician involvement at the time of the vaccination. Standing orders are implemented in settings such as clinics, hospitals, and long-term care facilities. Standing orders have had positive effects on vaccination coverage among children and adults.

Standing order protocols should:

- Identify persons eligible for vaccination based on their age, their immunization status, or the presence of a medical condition putting them at high risk.
- Provide adequate information to patients or their parents regarding the risks and benefits of a vaccine and document the delivery of that information.
- Record patient refusals or medical contraindications.
- Record administration of a vaccine(s) and any postvaccination adverse events, according to institution- or physician-approved protocol.
- Provide documentation of vaccine administration to patients and their primary care providers.

Standing order protocols should also specify that vaccines be administered by health care personnel trained in screening patients for contraindications to vaccination, administering vaccines correctly, and monitoring patients for adverse events in accordance with state and local regulations.

NOTES

NOTES

Staff Education

Anyone responsible for administering vaccines should be knowledgeable about immunization principles, scheduling, safety and effectiveness, and proper administration techniques. Starting with the front office, each staff member should be aware of the importance of vaccines, educated on proper immunization practices and recommendations, and prepared to answer patient questions as related to their position. Numerous educational materials in a variety of formats are available from CDC and some state, local, and territorial health departments, hospitals, and other professional organizations.

Record-Keeping

Patient records are essential to a medical practice, and maintaining these records remains a critical part of providing optimal health care. Immunization records in particular must be accurate and meet all applicable legal requirements, as well as requirements of any specific program (such as the VFC program) in which the provider participates. These records should be available for compliance inspections and should be easy to interpret by anyone examining them.

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

Because patients often receive vaccines at more than one provider's office, communication between sites is essential for maintaining complete and accurate vaccination records. School-based, public health, and community-based vaccination sites should communicate with primary care personnel through quick and reliable methods. IISs provide the most seamless and comprehensive avenue for sharing information; however, e-mail, telephone, or fax can also be used. Using an IIS or other mechanism is increasingly important as more venues outside the medical home offer vaccinations.

Acknowledgements

The editors would like to acknowledge Jennifer Hamborsky, Ginger Redmon, Tom Shimabukuro, and Skip Wolfe for their contributions to this chapter.

Selected References

American Academy of Pediatrics, Committee on Community Health Services and Committee on Practice and Ambulatory Medicine. Increasing Immunization Coverage. *Pediatrics* 2003;112:993–6.

Cataldi J, Kerns M, O'Leary S. Evidence-based strategies to increase vaccination update: a review. *Curr Opin Pediatr* 2020;32(1):151–9.

Dietz V, Baughman A, Dini E, et al. Vaccination practices, policies, and management factors associated with high vaccination coverage levels in Georgia public clinics. *Arch Pediatr Adolesc Med* 2000;154:184–9.

Dini E, Linkins R, Sigafoos J. The impact of computer-generated messages on childhood immunization coverage. *Am J Prev Med* 2000;18(2):132–9.

Lau M, Lin H, Flores G. Factors associated with human papillomavirus vaccine-series initiation and healthcare provider recommendation in U.S. adolescent females: 2007 National Survey of Children's Health. *Vaccine* 2012;30:3112–8.

LeBaron C, Mercer J, Massoudi M, et al. Changes in clinic vaccination coverage after institution of measurement and feedback in 4 states and 2 cities. *Arch Pediatr Adolesc Med* 1999;153:879–86.

National Vaccine Advisory Committee. Standards for child and adolescent immunization practices. *Pediatrics* 2003;112:958–63.

National Vaccine Advisory Committee. Recommendations from the National Vaccine Advisory Committee: Standards for Adult Immunization Practice. *Public Health Reports* 2014;129:115–23.

Nour R. A systematic review of methods to improve attitudes towards childhood vaccinations. *Cureus* 2019;11(7):e5067.

Poland G, Shefer A, McCauley M, et al. Standards for adult immunization practices. *Am J Prev Med* 2003;25:144–50.

NOTES

NOTES

Task Force on Community Preventive Services. *Guide to Community Preventive Services*. Washington D.C.: HHS Online. Available at http://www.thecommunityguide.org.

Vielot N, Islam J, Sanusi B, et al. Overcoming barriers to adolescent vaccination: perpectives from vaccine providers in North Carolina. *Women Health* 2020;Aug9:1–12.

Walker T, Elam-Evans L, Yankey D, et al. National, Regional, State, and Selected Local Area Vaccination Coverage Among Adolescents Aged 13–17 Years — United States, 2018. *MMWR* 2019;68:718–23.

Yitalo K, Lee H, Mehta, N. Health care provider recommendation, human papillomavirus vaccination, and race/ethnicity in the U.S. National Immunization Survey. *Am J Public Health* 2013;103(1):164–9.

A. Patricia Wodi, MD and Tom Shimabukuro, MD, MPH, MBA

The United States' long-standing vaccine safety program closely and constantly monitors the safety of vaccines. This chapter describes how vaccines licensed for use in the United States are monitored for safety and presents general information about the health care provider's role in immunization safety.

Adverse Events Following Immunization and Assessment of Causality

An adverse event following immunization refers to any medical event that occurs after vaccination. The adverse event may or may not be related to immunization. Further assessment is needed to determine if an adverse event is caused by a vaccine. A vaccine adverse reaction or side effect is an untoward effect caused by a vaccine.

Adverse events following immunization can be classified by frequency (common, rare), extent (local, systemic), severity (mild, moderate, severe), seriousness (life-threatening, requiring hospitalization, or causing disability or death), causality, and preventability (intrinsic to vaccine, production challenge, administration error). Adverse events following immunization may be coincidental, or the vaccine may have increased the risk of the adverse event. Many adverse events following vaccination are coincidental; they are temporally related to vaccination but occur by chance without a causal relationship.

To assess causality of an adverse event following immunization, a great deal of information is generally needed. An adverse health event can be causally attributed to a vaccine more readily if:

- The health problem occurs during a plausible time period following vaccination.
- The adverse event corresponds to adverse events previously associated with the vaccine.
- The event is consistent with a specific clinical syndrome where association with vaccination has strong biologic plausibility (e.g., anaphylaxis) or where the syndrome is known to occur following the natural disease.
- A laboratory result confirms the association (e.g., isolation of vaccine-strain varicella virus from skin lesions of a patient with rash).
- The event recurs with re-administration of the vaccine in the same patient.

NOTES

NOTES

- A controlled clinical trial or epidemiologic study shows greater risk of a specific adverse event among vaccinated versus unvaccinated groups.
- A finding linking an adverse event to a vaccine has been confirmed by other studies.

Importance of Vaccine Safety Programs

Like any medical product, no vaccine is completely without risk. While most vaccine adverse reactions are minor and self-limited, some vaccines have been associated with extremely rare but serious health effects. The following key considerations underscore the need for an active and ongoing vaccine safety program.

Decreases in Disease Risks

Most vaccine-preventable diseases are at or near record lows. Many people no longer see reminders of the severity and potential life-threatening complications of these diseases. Parents and providers in the United States may be more likely to know someone who has experienced an adverse event (an event that may or may not be related to vaccination) following vaccination than they are to know someone who has experienced a vaccine-preventable disease. The success of vaccination has led to increased public attention on potential health risks associated with vaccines.

Public Confidence

Maintaining public confidence in vaccines is critical to prevent a decline in vaccination coverage that can result in outbreaks of disease. While most parents understand the benefits of vaccination and have their children vaccinated, some parents have concerns about the safety of vaccines. Despite high national vaccination coverage, there are local areas of low coverage that allow outbreaks of vaccine-preventable diseases to occur, often the result of parents refusing or delaying their children's vaccinations because of concerns about vaccine safety.

A higher standard of safety is generally expected of vaccines than of other medical interventions because, in contrast to most pharmaceutical products that are administered to ill persons for treatment purposes, vaccines are generally administered to healthy persons to prevent disease. Public tolerance for adverse reactions related to products given to healthy persons, especially healthy infants and children, is substantially less than for reactions to products administered to persons who are already sick. Less tolerance of risk associated with vaccines requires close monitoring and timely assessment of vaccine adverse events to help distinguish true vaccine adverse reactions from coincidental unrelated events and to help maintain public confidence in vaccination.

Balancing Immunization Recommendations with Risk of Disease

Public health recommendations for immunization programs and practices represent a dynamic balance of risks and benefits. Vaccine safety monitoring is necessary to accurately weigh this balance and adjust immunization policy. For example, monitoring of smallpox and oral polio vaccines being used in the United States as these diseases neared global eradication found complications associated with each vaccine that exceeded the risks of the diseases. This observation led to discontinuation of routine smallpox vaccination in the United States prior to global eradication and a shift from the oral poliovirus vaccine to a safer, inactivated poliovirus vaccine.

Assessing and 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 adverse reactions. Phase II trials generally enroll hundreds of volunteers and determine the best dose and number of doses for effectiveness and safety. Phase I and II trials might take a few months or last up to three years. Phase III trials involve a few hundred to several thousand volunteers and may last several years. Some volunteers receive another vaccine that has already been licensed, allowing researchers to compare one vaccine with another for adverse health effects, anything from a sore arm to a serious reaction. If the vaccine is shown to be safe and effective in a Phase III trial, the manufacturer applies for a license from the Food and Drug Administration (FDA). During the application process, the FDA reviews the clinical trial results, product labeling, and manufacturing plant and protocols. If approved, the FDA licenses the vaccine itself (product license) and licenses the manufacturing plant where the vaccine will be produced (establishment license).

Postlicensure Vaccine Safety Monitoring

Monitoring for adverse reactions is essential even after vaccine licensure because rare reactions, delayed reactions, or reactions among subpopulations may not be detected before vaccines are licensed. While Phase III trials include enough persons to identify certain potential adverse reactions, such as injection-site reactions and fever, the comparatively small number of patients enrolled in these trials generally limits detection of rare adverse reactions, including those occurring many months after the vaccine is administered. For example, in the pentavalent

NOTES

NOTES

rotavirus vaccine trials, 70,000 infants received either vaccine or placebo, permitting evaluation of safety with respect to intussusception, which occurs so rarely that large trials would be needed to detect even a single occurrence.

The objectives of postlicensure vaccine safety monitoring activities are to:

- Identify rare adverse reactions not detected during prelicensure studies.
- Monitor increases in known adverse reactions after vaccination.
- Identify risk factors or preexisting conditions that may be associated with a higher incidence of adverse reactions.
- Identify whether particular vaccine lots have unusually high rates or certain types of reactions.
- Identify possible adverse events that might warrant further study to establish the association of an adverse event with vaccination or affect current immunization recommendations.

To achieve these objectives, as part of the FDA approval process, some vaccines enter Phase IV clinical trials (postmarketing studies) to obtain information beyond what Phases I through III provided. Also, fundamental to preventing safety problems is the assurance that all vaccines are made using good manufacturing practices and undergo lot testing for purity and potency. Manufacturers must submit samples of each vaccine lot and results of their own tests for purity and potency to the FDA before releasing vaccine lots for public use. Several monitoring systems are used in the United States to detect and study adverse events following immunization. CDC and the FDA use four main systems to monitor the safety of vaccines in use: the Vaccine Adverse Event Reporting System (VAERS), the Vaccine Safety Datalink (VSD), the Postlicensure Rapid Immunization Safety Monitoring System (PRISM), and the Clinical Immunization Safety Assessment (CISA) project.

Vaccine Adverse Event Reporting System (VAERS)

The National Childhood Vaccine Injury Act of 1986 mandates that vaccine providers and vaccine manufacturers report certain adverse events following vaccinations. This led to the creation of the Vaccine Adverse Event Reporting System (VAERS) in 1990. VAERS is a national, spontaneous surveillance system, jointly administered by CDC and the FDA. It receives about 30,000 reports per year, a seemingly large number, but relatively small considering that millions of doses of vaccines are administered yearly to adults and children in the United States.

Vaccine providers are required by law to report:

- Any adverse event listed by the vaccine manufacturer as a contraindication to further doses of the vaccine
- Any adverse event listed in the VAERS Table of Reportable Events Following Vaccination (vaers.hhs.gov/resources/VAERS_Table_of_Reportable_Events_Following_Vaccination.pdf)

Vaccine providers are encouraged to report:

- Any adverse event that occurs after the administration of a U.S. licensed vaccine, whether it is or is not clear a vaccine caused the adverse event
- Vaccine administration errors

Vaccine manufacturers are required to report all adverse events that come to their attention.

VAERS collects information about the patient, the vaccine(s) administered, the adverse event, and the person reporting the event. All reports are coded using Medical Dictionary for Regulatory Activities (MedDRA) terms and entered into the VAERS database. Attempts are made to obtain additional medical information for all reports classified as a serious adverse event, including hospitalization or prolongation of hospitalization (if a vaccine was administered in the hospital), life-threatening illness, permanent disability, congenital deformity, or death. For these reports, letters to obtain information about recovery status are also sent to the persons reporting the events. All patient-identifying information submitted to VAERS, directly or as part of follow-up activities, is protected by strict confidentiality requirements.

VAERS has limitations inherent to spontaneous reporting systems. Also, VAERS is not designed to determine if a vaccine caused an adverse event, and additional studies are required to confirm possible safety signals detected by VAERS.

Despite these limitations, VAERS has been able to fulfill its primary purpose of detecting new or rare vaccine adverse events, increases in rates of known adverse reactions, and patient risk factors for types of adverse reactions. In addition, VAERS often provides early safety data after a vaccine is licensed or during a public health emergency. De-identified VAERS reports can be viewed on the VAERS web page.

NOTES

NOTES

Vaccine Safety Datalink (VSD)

CDC established the VSD to address gaps in the scientific knowledge of rare and serious adverse events following vaccination. This project involves partnerships with large, integrated health plans to monitor vaccine safety. Each participating plan uses its electronic health records and immunization information systems to contribute to a large, linked database. These participating health plans serve more than 10 million people annually, representing nearly 3% of the U.S. population, and contain records for more than 180 million vaccinations, enabling the VSD to study possible rare adverse events. Available information includes vaccination data (vaccine type, vaccination date, concurrent vaccinations), health conditions, medical encounter types (outpatient, inpatient, urgent care), birth data, and census data.

The VSD allows for planned immunization safety studies, as well as timely investigations of hypotheses arising from review of medical literature, reports to VAERS, changes in immunization schedules, or the introduction of new vaccines. A rapid cycle analysis conducted by the VSD enables CDC and its co-investigators to monitor adverse events following vaccination for a specific disease in near real time, so the public can be informed quickly of possible risks.

Data files used in VSD studies remain at each participating site; specific data are pulled together for each analysis and do not contain personal identifiers.

Clinical Immunization Safety Assessment (CISA) Project

The CISA Project's mission is to improve the understanding of adverse events following immunization at the individual patient level. The CISA Project provides consultation to public health partners in the United States and conducts high-quality clinical research, including clinical trials across life stages, on the safety of influenza vaccines and the safety of vaccines in special populations. All clinical research studies conducted by the CISA Project are registered on clinicaltrials.gov.

The goals of the CISA Project are to:

- Serve as a vaccine safety resource for U.S. healthcare providers with complex vaccine safety questions about a specific patient to assist with immunization decision-making
- Assist CDC / Health and Human Services (HHS) and partners in evaluating emerging vaccine safety issues
- Conduct clinical research studies to better understand vaccine safety and identify preventive strategies for adverse events following immunization

Postlicensure Rapid Immunization Safety Monitoring System (PRISM)

FDA's PRISM uses a computer algorithm to conduct active vaccine safety surveillance. A cooperative effort between FDA's Center for Biologics Evaluation and Research and four health care and medical insurance organizations, PRISM analyzes health insurance claims data for potential vaccine safety signals. PRISM is also used to evaluate safety issues in targeted groups and to evaluate specific health conditions or outcomes.

PRISM is part of FDA's Sentinel Initiative, a national electronic system for medical product safety surveillance.

Vaccine Injury Compensation Program (VICP)

A main impact of the National Childhood Vaccine Injury Act (NCVIA) was the creation of the VICP. This program, administered by the Health Resources and Services Administration, provides financial compensation to persons who are found to have been injured by a vaccine covered by the program. VICP provides liability protection for vaccine manufacturers and administrators. Compensation is provided to persons who experience certain vaccine adverse reactions on a no-fault basis. No fault means persons filing claims are not required to prove negligence on the part of either the health care provider or manufacturer to receive compensation. The program covers most vaccines routinely given in the United States.

Claims may be based on a *Vaccine Injury Table*, which lists conditions associated with each vaccine and provides a rebuttable presumption of causation, or by proving by preponderant evidence that the vaccine caused an injury not listed in the table. The *Vaccine Injury Table* was developed initially by Congress to provide swift compensation to persons possibly injured by vaccines. The table continues to be amended by the Secretary of the Department of Health and Human Services (DHHS) to better reflect current science as more information becomes available from research on vaccine adverse reactions.

During the 2009 H1N1 influenza pandemic, the federal government implemented another compensation program, the Countermeasures Injury Compensation Program (CICP). This program provides compensation for certain persons who are seriously injured by countermeasures as specified in a declaration by the Secretary of DHHS. Both bioterrorism and pandemic countermeasures are covered. Covered countermeasures within the CICP are not limited to vaccines and may include certain medications or devices used to diagnose, prevent, or treat the covered condition. People have one year from receipt of the countermeasure to file a claim with the CICP.

NOTES

NOTES

The Vaccination Provider's Role in Vaccine Safety

Even though the testing phases to approve a vaccine can take years before the vaccine can be licensed and vaccines are monitored continually for safety and effectiveness, vaccination providers also play a key role in helping to ensure the safety and efficacy of vaccines. Vaccine providers are responsible for proper vaccine storage, handling, and administration; timing and spacing of vaccine doses; observation of contraindications and precautions; and reporting of adverse events following vaccination to VAERS. Providers are also responsible for communicating with patients and parents about vaccine benefits and risks and for managing of vaccine adverse reactions.

Benefit and Risk Communication

Patients and parents should be informed of the benefits and risks of vaccines in understandable language. An 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 NCVIA legally requires vaccine information statements (VISs) be provided to the patient, parent, guardian, or legal representative by vaccine providers before each dose of vaccine. Documentation that the VIS was provided is also required. Copies of VISs are available from state and local immunization programs or can be downloaded from https://www.cdc.gov/vaccines/hcp/vis/index.html. Translations of VISs into languages other than English are available from some immunization programs and the Immunization Action Coalition and are available at https://immunize.org/vis/.

Vaccine providers should anticipate questions parents or patients may have regarding the need for or safety of vaccination. Some people may refuse certain vaccines or even reject all vaccinations. Some people might have religious or personal objections to vaccination. It is essential that health care providers have a basic understanding of how patients view vaccine risk and develop effective approaches to deal with vaccine safety concerns when they arise. When a parent or patient initiates discussion of a vaccine concern, the provider should discuss the specific concern and use appropriate language to provide facts. Effective, empathic vaccine risk communication is essential in responding to misinformation and concerns. It is important to remind parents that state laws for school or childcare entry might require

unvaccinated children to stay home from school during outbreaks. For patients who question or refuse vaccination, identifying common ground and discussing measures for deferring vaccination are more effective public health strategies than excluding these patients from a practice.

VISs provide an outline for discussing vaccine benefits and risks. While documentation of VIS distribution is required, additional information about discussions should be documented in the patient's record, including the refusal to receive certain vaccines (i.e., informed refusal). Such documentation might reduce any potential liability if a vaccine-preventable disease occurs in the unvaccinated patient.

Managing Adverse Reactions after Vaccination

Health care providers should be familiar with identifying immediate-type allergic reactions, including anaphylaxis, and be competent in treating these events at the time of vaccine administration. While severe allergic reactions to vaccines are rare, occurring at an approximate rate of one to two for every 1 million doses of vaccine administered, all vaccine providers should have emergency procedures in place and be prepared to provide emergency care for a person who experiences an anaphylactic reaction. This includes the ability to administer epinephrine and certification in cardiopulmonary resuscitation (CPR). Equipment for maintaining an airway should be available for immediate use. All health care personnel should be familiar with their office emergency plan.

NOTES

NOTES

Acknowledgements

The editors would like to acknowledge Jennifer Hamborsky, Andrew Kroger, Michael McNeil, Valerie Morelli, John Su, and Eric Weintraub for their contributions to this chapter.

Selected References

American Academy of Pediatrics. Vaccine Safety. In: Kimberlin D, Brady M, Jackson M, et al., eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics;2018:41–54.

Berger B, Omer S. Could the United States experience rubella outbreaks as a result of vaccine refusal and disease importation? *Human Vaccines* 2010;6(12):1016–20.

Bohlke K, Davis R, Marcy S, et al. Risk of anaphylaxis after vaccination of children and adolescents. *Pediatrics* 2003;112(4):815–20.

CDC. *General Best Practice Guidelines for Immunization: Best Practices Guidance of the Advisory Committee on Immunization Practices (ACIP)*. (www.cdc.gov/vaccines/hcp/acip-recs/general-recs/downloads/general-recs.pdf). Accessed December 27, 2019 and August 12, 2020.

CDC. Measles cases and outbreaks. https://www.cdc.gov/measles/cases-outbreaks.html. Accessed August 2, 2017 and August 16, 2020.

CDC. Suspension of rotavirus vaccine after reports of intussusception—United States, 1999. *MMWR* 2004;53(34):786–9.

Iskander J, Miller E, Chen R. The role of the Vaccine Adverse Event Reporting System (VAERS) in monitoring vaccine safety. *Pediatr Ann* 2004;33(9):599–606.

Shimabukuro T, Nguyen M, Martin D, et a. Safety monitoring in the Vaccine Adverse Event Reporting System (VAERS). *Vaccine* 2015;33(36):4398–405.

Slade B, Leidel L, Vellozzi C, et al. Postlicensure safety surveillance for quadrivalent human papillomavirus recombinant vaccine. *JAMA* 2009;302(7):750–7.

Su J, Moro P, Ng C, et al. Anaphylaxis after vaccination reported to the Vaccine Adverse Event Reporting System, 1990-2016. *J Allergy Clin Immunol* 2019; 143(4):1465–73.

Vellozzi C, Broder K, Haber P, et al. Adverse events following influenza A (H1N1) 2009 monovalent vaccines reported to the Vaccine Adverse Event Reporting System, United States, October 1, 2009–January 31, 2010. *Vaccine* 2010;28(45):7248–55.

Storage and Handling

Tina Objio, RN, MSN; Valerie Morelli, BA; and Sean Trimble, BS, MPH

This chapter provides an overview of best practice guidance for storage and handling. CDC's *Vaccine Storage and Handling Toolkit* contains detailed information on best practices and recommendations. Participants in the Vaccines for Children (VFC) program or providers with vaccines purchased with public funds should consult their state or local immunization program to ensure all state storage and handling requirements are met, since there may be requirements that are specific to or tailored to the jurisdiction.

Vaccine Cold Chain

A cold chain is a temperature-controlled supply chain that includes all vaccine-related equipment and procedures. The cold chain begins with the cold storage unit at the manufacturing plant, extends to the transport and delivery of the vaccine and proper storage at the provider facility, and ends with administration of the vaccine to the patient.

Manufacturers, distributors, public health staff, and health care providers share responsibility to ensure the vaccine cold chain is maintained from the time vaccines are manufactured until they are administered.

Vaccine Storage and Handling Standard Operating Procedures (SOPs)

Facilities should develop and maintain clearly written, detailed, and up-to-date storage and handling standard operating procedures (SOPs). SOPs should be reviewed by all staff and updated by the vaccine coordinator annually.

SOPs should contain plans and information for three major areas:

- General information – include contact information for vaccine manufacturers, equipment service providers, and important facility staff, as well as job descriptions, regularly used forms, and staff training requirements.
- Routine storage and handling – include information for all aspects of vaccine inventory management, from ordering to monitoring storage conditions.
- Emergency vaccine storage, handling, and transport – outline steps to be taken in the event of equipment malfunctions, power failures, natural disasters, or other emergencies that might compromise vaccine storage conditions.

VFC providers or those who have vaccines purchased with public funds should contact their immunization program for guidance regarding routine and emergency SOPs.

NOTES

NOTES

Staff Training

All staff members who receive deliveries or handle vaccines should be trained in proper storage and handling as described in the facility's SOPs. SOPs should be kept near vaccine storage units and staff should know where to find them.

Storage and handling training should be done:

- As part of new employee orientation
- Annually as a refresher for all staff involved in immunization activities
- When new vaccines are added to inventory
- When vaccine recommendations are updated

Vaccine Coordinator

A primary vaccine coordinator should be responsible for ensuring all vaccines are stored and handled correctly, with an alternate coordinator appointed who can serve in the absence of the primary coordinator. These individuals should be fully trained in routine and emergency policies and procedures. Coordinator responsibilities may be completed by the coordinator or delegated to appropriate staff. The coordinator must ensure the delegate has documented training demonstrating competency for the specific tasks assigned and must confirm that tasks are completed.

Some coordinator responsibilities include:

- Ordering vaccines
- Overseeing proper receipt and storage of vaccine deliveries
- Documenting vaccine inventory information
- Organizing and monitoring vaccines within storage units, including rotating stock and removing expired vaccines
- Setting up temperature monitoring devices (TMDs) and recording daily temperatures
- Responding to temperature excursions (out-of-range temperatures) and equipment failures
- Overseeing vaccine transport (when necessary)
- Overseeing emergency preparations
- Creating and updating storage and handling SOPs

Vaccine Storage and Temperature Monitoring Equipment

It is important for a facility to have proper storage and monitoring equipment that is set up correctly, maintained appropriately, and repaired as needed. This equipment protects patients from inadvertently receiving compromised vaccine and protects facilities against costs of revaccinating patients, replacing expensive vaccines, and losing patient confidence.

Refrigerators and Freezers

CDC recommends the following types of refrigerators and freezers:

- Purpose-built or pharmaceutical-grade units designed to either refrigerate or freeze biologics, including vaccines, are preferred. These units can be compact, under-the-counter style or large units.
- If a purpose-built or pharmaceutical-grade unit is not available, a stand-alone, household-grade unit may be an acceptable option in some practice settings. Only the refrigerator compartment of a household-grade combination refrigerator/freezer unit should be used. The freezer compartment of this type of unit is not recommended for storing vaccines and there may be areas of the refrigerated compartment that should not be used as well. These units have cold spots and temperature fluctuations, and air circulating from the freezer could expose refrigerated vaccines to freezing temperatures. A separate freezer unit is necessary for storage for facilities that stock frozen vaccines.

All units should have enough space to store the largest inventory expected at the busiest point in the year (e.g., flu season) without crowding.

Never store any vaccine in a dormitory-style or bar-style combined unit. These units often have a single exterior door and an evaporator plate/cooling coil, usually located in an icemaker/freezer compartment. These units pose a significant risk of freezing vaccines, even when used for temporary storage.

Temperature Monitoring Devices (TMDs)

Every vaccine storage unit must have a reliable TMD. CDC recommends (and VFC requires) the use of a continuous monitoring and recording device called a "digital data logger" (DDL), set at recording intervals of at least every 30 minutes. Many DDLs use a buffered temperature probe. Temperatures measured by a buffered probe match vaccine temperature more closely than those measured by standard thermometers, which

NOTES

NOTES

tend instead to reflect air temperature. DDLs provide details on how long a unit has been operating outside the recommended temperature range (a temperature excursion). Each DDL should have a current and valid Certificate of Calibration Testing (also known as a "Report of Calibration") to ensure device accuracy.

DDLs should have the following characteristics:

- Detachable probe that best reflects vaccine temperatures (e.g., a probe buffered with glycol, glass beads, sand, or Teflon®)
- Alarm for out-of-range temperatures
- Low-battery indicator
- Current, minimum, and maximum temperature display
- Recommended uncertainty of +/-0.5°C (+/-1°F)
- Logging interval (or reading rate) that can be programmed by the user to measure and record temperatures at least every 30 minutes

Temperature data from a DDL can be downloaded to a computer using special software or retrieved from a website for user review, which is critical to ensuring vaccine safety. The software or website may also allow the user to set the frequency of temperature readings.

Each facility should have a recommended TMD for:

- Each vaccine storage unit
- Each emergency transport unit
- Backup (with a different calibration testing schedule) in case a primary device malfunctions or is out for calibration testing

Calibration testing should be done every one to two years or according to the manufacturer's suggested timeline. CDC recommends that a DDL's current and valid Certificate of Calibration Testing include:

- Model/device name or number
- Serial number
- Date of calibration (report or issue date)
- Confirmation that the instrument passed testing (or instrument in tolerance)
- Recommended uncertainty of +/-0.5°C (+/-1°F) or less

Storage Unit Setup

Storage units should be placed in a well-ventilated room, leaving space between the unit, ceiling, and any wall. Nothing should block the cover of the motor compartment. The unit should be firm and level, with the bottom of the unit above the floor. The unit door should open and close smoothly and fit squarely against the body of the unit. Studies find that most units work best when placed in an area with standard indoor room temperatures, usually considered to be between 20°C and 25°C (68°F and 77°F). Check the manufacturer-supplied owner's manual for additional guidance on placement and spacing.

Stabilizing Temperatures

It may take two to seven days to stabilize the temperature in a newly installed or repaired refrigerator and two to three days to stabilize the temperature for a freezer.

Before using a unit for vaccine storage, the minimum and maximum temperatures each workday for two to seven days should be checked and recorded. If temperatures cannot be recorded digitally, they should be checked and recorded a minimum of two times each workday. Once two consecutive days of temperatures have been recorded within the recommended range, the unit is stable and ready for use.

Power Supply

To protect the storage unit's power supply:

- Plug in only one storage unit per electrical outlet.
- Use a safety-lock plug or an outlet cover to prevent the unit from being unplugged.
- Post "DO NOT UNPLUG" warning signs at outlets and on storage units to alert staff, custodians, electricians, and other workers not to unplug units.
- Label fuses and circuit breakers to alert people not to turn off power to storage units.
- Use caution when using power outlets that can be tripped or switched off and avoid using built-in circuit switches (that may have reset buttons), outlets activated by a wall switch, and multioutlet power strips.

NOTES

NOTES

Equipment Maintenance

Storage units and temperature monitoring devices need regular maintenance to ensure proper operation, maintain required temperatures, and extend the useful life of the equipment.

- Check storage unit door seals regularly for signs of wear and tear.
- Check door hinges and adjust so that the door opens and closes smoothly and fits squarely against the body of the unit. Leaving the door open can cause the thermostat to respond to warmer room temperatures, and the unit will work harder to maintain the correct temperature inside. The temperature may become very cold in some parts of the unit. Using an open-door alarm and a self-closing door may be helpful.
- Clean unit coils and motor per manufacturer instructions.
- Clean inside of units to discourage bacterial and fungal growth. Cleaning must be done quickly to minimize the risk of the temperature going out of range.
- Defrost manual-defrost freezers when the frost exceeds either 1 cm or per the manufacturer's suggested limit. Follow the manufacturer's instructions. While defrosting, store vaccines temporarily in another unit with appropriate freezer temperatures.
- Temperature monitoring devices experience "drift" over time that affects accuracy. If calibration testing indicates the device is no longer accurate within +/-0.5°C (+/-1°F), it should be replaced. Adjustments to correct accuracy are not recommended.
- Storage unit temperatures may need to be adjusted over time. Temperature adjustments should only be made by a vaccine coordinator and not during a busy part of the workday when the door is being frequently opened. The coordinator should confirm there is not another issue (e.g., unit unplugged, door left open, broken TMD, etc.) before making any adjustment to the temperature.
- If you believe there could be an issue with the TMD, use the backup TMD to confirm the temperature before making any adjustments.

If a backup generator is used, it should be tested quarterly and serviced annually, and according to the manufacturer's guidance.

Organizing and Storing Vaccine in Storage Unit

Manufacturers' package inserts should be referred to for the most up-to-date storage and handling recommendations for specific vaccines and diluents.

Storing Vaccine

To confirm vaccines are stored correctly and to minimize the risk of administration errors:

- Store vaccines in their original packaging with lids closed in separate containers until ready for administration to protect them from light and provide additional thermal stability/protection. Never store loose vials or manufacturer-filled syringes outside of their packaging. This increases the risk of administration errors, exposes vaccine to light, and makes it more difficult to track expiration dates and manage inventory. For certain purpose-built units, it is recommended that vaccine be stored outside of the packaging. If this is the case, follow the manufacturer's guidance for vaccine storage.
- Place vaccines and diluents with the earliest expiration dates in front of those with later expiration dates.
- Store vaccines and diluents with similar packaging or names or with pediatric and adult formulations on different shelves.
- Whenever possible, store diluent with the corresponding refrigerated vaccine. Never store diluent in a freezer.
- Position vaccines and diluents two to three inches from the unit walls, ceiling, floor, and door.
- Arrange vaccines and diluents in rows and allow space between them to promote air circulation.
- If using a household-grade unit, avoid storing vaccines and diluents in any part of the unit that may not provide stable temperatures or sufficient air flow, such as directly under cooling vents; in deli, fruit, or vegetable drawers; or on refrigerator door shelves.
- Place water bottles on the top shelf, the floor, and in the door racks of a household-grade unit. Putting water bottles in the unit can help maintain stable temperatures. (Water bottles are not recommended for use with certain pharmaceutical-grade units, follow manufacturer's directions.)

NOTES

NOTES

- Avoid placing or storing any items other than vaccines, diluents, and water bottles inside storage units. If other medications and biological products must be stored in the same unit as vaccines, they must be clearly marked and stored in separate containers or bins from vaccines. Potentially contaminated items (e.g., blood, urine, stool) should be properly contained and stored below vaccines to avoid contamination from drips or leaks.
- Place the TMD in the center of the unit with the vaccines surrounding it. A DDL should be set to measure temperature no less frequently than every 30 minutes.

Temperature Ranges

Refrigerators should maintain temperatures between 2°C and 8°C (36°F and 46°F). Freezers should maintain temperatures between -50°C and -15°C (-58°F and +5°F). Refrigerator or freezer thermostats should be set at the factory-set or midpoint temperature, which will decrease the likelihood of temperature excursions.

Thermostats are marked in various ways and, in general, show levels of coldness rather than temperatures. The only way to know the temperature where vaccines are stored is to measure and monitor it with a TMD.

Monitoring Vaccine Temperatures

To ensure the safety of vaccines, the storage unit minimum and maximum temperatures should be checked and recorded at the start of each workday. If using a TMD that does not display minimum and maximum temperatures, then the current temperature should be checked and recorded a minimum of two times (at the start and end of the workday).

A temperature monitoring log sheet should be placed on each storage unit door (or nearby), and the following information should be recorded:

- Minimum/maximum temperature (or current temperature if using a device that does not record minimum/maximum temperatures)
- Date
- Time
- Name of person who checked and recorded the temperature
- Any actions taken if a temperature excursion occurred

If a reading is missed, leave a blank entry in the log. Such entries should be distinguished from entries in which the TMD failed to display a reading.

Check unit doors throughout the day and always at the end of the day to ensure they are tightly closed.

On a weekly basis, review storage unit temperature readings for changes in temperature trends that might require action (adjusting unit temperature or repairing/replacing storage or temperature monitoring equipment). Temperature data should be kept for three years (unless state statutes or rules require a longer period).

Temperature Excursions (Out-of-Range Temperatures)

Any temperature reading outside ranges recommended in the vaccine manufacturers' package inserts is considered a temperature excursion and requires immediate action:

1. Notify the primary or alternate vaccine coordinator immediately or report the problem to a supervisor.
2. Label exposed vaccines "DO NOT USE," and place them in a separate container apart from other vaccines in the storage unit (do not discard these vaccines).
3. The vaccine coordinator or supervisor should begin to document details of the event.
4. Implement your facility's SOPs for temperature excursions, being sure to check temperature monitoring device placement or adjusting unit temperature as needed.
5. Contact your immunization program and/or the vaccine manufacturer(s) per your SOPs for guidance.
6. Complete documentation of the event, including actions taken and results.

Vaccines should never remain in a nonfunctioning unit for an extended period. If it is believed a unit has failed, implementation of emergency SOPs should begin.

NOTES

NOTES

Vaccine Inventory Management

It is important to make sure vaccines are unpacked and stored correctly and to account for every dose received and used, whether administered, wasted, compromised, expired, or transferred.

Deliveries

Scheduling and Receiving Deliveries

The vaccine coordinator or alternate should be notified immediately when vaccines arrive. Vaccines should be unpacked and stored immediately. Vaccine delivery should only be scheduled on dates and during times staff will be present. A vaccine delivery container should never be left unattended.

Unpacking Deliveries

Vaccines and diluents should be unpacked and promptly stored at recommended temperatures. They should not be stored in an unopened shipment box.

- Examine the shipping container and contents for signs of damage.
- Compare contents against the packing list. For frozen vaccines, the packing list may show the maximum time vaccines can be in transit based on shipment date.
- Ensure that lyophilized vaccines came with the correct type and quantity of diluents.
- Check vaccine and diluent expiration dates to ensure there are no expired or soon-to-expire products.
- If included, check the cold chain monitor (CCM) for any temperature excursion during transit. Note: CCMs are for one-time use and should be discarded after being checked.

If there are discrepancies between the contents and the packing list or other concerns about the contents (including temperature excursion), the vaccine manufacturer should be immediately notified. If a temperature excursion is suspected, vaccines should be labeled "DO NOT USE" and stored in the appropriate vaccine storage unit, separated from other vaccines, until a vaccine viability determination is made. The state or local immunization program should be contacted regarding any VFC or other vaccines purchased with public funds.

Inventory Accounting

Conduct a vaccine inventory assessment at least once a month and before placing vaccine orders to ensure adequate vaccines and diluents are on hand. Determining factors for ordering include projected demand, storage capacity, and current vaccine supplies. Many state and local immunization information systems (IISs) have vaccine inventory accounting functions and VFC providers may be required to use the IIS to track inventory.

Stock Rotation and Removal

Vaccine stock should be rotated and checked for expired doses regularly. Any expired vaccines and diluents should be removed immediately to avoid inadvertently administering them.

Understanding Expiration Dates

Determining when a vaccine or diluent expires is an essential step in proper vaccine storage and handling. Administration of expired vaccine remains one of the top vaccine storage and handling errors, so it is crucial for staff to understand how to read expiration dates to prevent patients from receiving invalid vaccine doses.

When the expiration date has only a month and year, the product may be used up to and including the last day of that month. If a day is included with the month and year, the product may only be used through the end of that day. Products that have been contaminated or compromised should not be used, regardless of the expiration date.

In some instances, such as when a manufacturer indicates there is a beyond-use date (BUD), vaccines must be used before the expiration date on the label.

The BUD is calculated based on the date the vial is first punctured and the storage information in the package insert. If the vaccine has no BUD, the vaccine should be used by the expiration date indicated by the manufacturer.

The BUD replaces the expiration date and should be noted on the label, along with the initials of the person making the calculation. Examples include:

- Reconstituted vaccines have a limited time frame for use once the vaccine is mixed with a diluent. For example, if the package insert states that the reconstituted vaccine must be used within 30 minutes, it must be discarded if not used by that time. This time frame might only apply as long as the reconstituted vaccine is still in the vial, not after it is drawn into a syringe, so the package insert should be carefully checked.

NOTES

NOTES

- Multidose vials (MDVs) might have a specified time frame for use once they have been entered with a needle. For example, the package insert may state that the vaccine must be discarded 28 days after it is entered. If the vial is entered on June 1, 2020, the BUD is June 29, 2020.
- Manufacturer-shortened expiration dates may apply when vaccine is exposed to inappropriate storage conditions. The manufacturer might determine that the vaccine can still be used but will expire on an earlier date than the date on the label.

In addition to a BUD, some MDVs have a specific number of doses that can be withdrawn. Once the maximum number of doses has been removed, the vial should be discarded, even if there is residual vaccine in the vial.

Vaccine and Equipment Disposal

Sometimes unused vaccine and diluent doses, unopened vials, expired vials, and potentially compromised vaccine may be returned for credit, even if they must be discarded. The state or local immunization program or the vaccine manufacturer can provide vaccine-specific information.

Open and broken vials and syringes, manufacturer-filled syringes that have been activated, and vaccines predrawn by providers cannot be returned and should be discarded according to state requirements.

Immediately after use, all syringe/needle devices should be placed in biohazard containers that are closable, puncture-resistant, leakproof on sides and bottom, and labeled or color-coded. This practice helps prevent accidental needlesticks and reuse. Used needles should not be recapped, cut, or detached from syringes before disposal.

Empty, expired, or compromised vaccine vials are usually not considered hazardous or pharmaceutical waste and do not require disposal in a biomedical waste container. However, state requirements regarding disposal should be followed. Medical waste disposal requirements are set by state environmental agencies.

Predrawing Vaccines

Vaccines should be drawn up only at the time of administration. General-use syringes are designed for immediate administration, not for storage. Contamination and growth of microorganisms can occur in syringes with predrawn vaccine that does not contain a preservative. In addition, vaccine components may interact with polymers in a plastic syringe over time, potentially reducing vaccine potency. Predrawing vaccines can also result in vaccine waste.

Even for off-site clinics, vaccine manufacturers do not recommend predrawing vaccines. As an alternative, CDC recommends using manufacturer-filled syringes (MFSs) for large vaccination clinics.

If vaccines must be predrawn:

- Set up a separate administration station for each vaccine type to prevent medication errors.
- Draw up vaccines only after arriving at the clinic site or mass vaccination event.
- Each person administering vaccines should draw up no more than one MDV or 10 doses at one time.
- Monitor patient flow to avoid drawing up unnecessary doses.
- Predraw reconstituted vaccine into a syringe only when ready for administration.
- If a predrawn vaccine is not used within 30 minutes of being reconstituted, follow manufacturer guidance for storage conditions and time limits.

Any remaining vaccine in predrawn syringes should be discarded at the end of the workday. Predrawn, reconstituted vaccine should never be transferred back into a vial for storage.

Vaccine Transport

To protect the vaccine supply, vaccine should be delivered directly to the facility where it will be used. However, sometimes, vaccine needs to be transported to an off-site or satellite facility for an event like an on-site vaccination clinic. Transport may also be required during emergencies such as long-term power outages or flooding or other natural disasters that can put the vaccine supply in jeopardy. In these instances, certain actions must be taken to protect the vaccine supply.

Vaccine transport to off-site or satellite facilities is different from both shipping and emergency transport. Shipping usually involves a professional carrier and a long distance and time frame for moving vaccines between locations. Transport involves the movement of vaccine over a short time frame and distance between providers. Depending on the situation, transport recommendations may vary. An organization's SOPs should clearly define transport procedures for all possible scenarios and should be used by trained staff for any vaccine transport.

NOTES

Preparing Vaccine for Transport

A facility should have a supply of materials needed for transport of the largest annual vaccine inventory.

Soft-sided containers specifically engineered for vaccine transport are acceptable (and may be part of a qualified container and packout system). Commercially available soft-sided food or beverage coolers should not be used because most are poorly insulated and likely to be affected by room or outdoor temperatures.

A TMD for each transport container should be used during transport, as well as appropriate coolants and transport materials according to the specific transport system(s) being used.

The same shipping containers the vaccines were initially shipped in may be used for emergency transport as a last resort only.

Partially used vials cannot be transferred between providers or across state lines.

Transport of Refrigerated Vaccines to Off-Site or Satellite Facilities

Best practices for transport include:

- The total time for transport alone or transport plus clinic workday should be a maximum of 8 hours.
- Transport diluents with their corresponding vaccines to ensure there are always equal amounts of vaccines and diluents for reconstitution.
- Transport only the amount of vaccine needed for the workday.
- If a noncommercial vehicle must be used, place the transport containers in the passenger compartment, not the trunk.

Transport System Recommendations

Container Description	Emergency Transport	Transport to Off-Site Clinic or Satellite Facility or for Relocation of Stock
Portable Vaccine Refrigerator or Freezer	Yes	Yes
Qualified Container and Packout	Yes	Yes
Conditioned Water Bottle Transport System*	Yes	No
Manufacturer's Original Shipping Container	Yes (last resort only)	No
Food/Beverage Coolers	No	No

*cdc.gov/vaccines/hcp/admin/storage/downloads/emergency-transport.pdf

Transport of Vaccines in Emergencies

In addition to the actions outlined above, in an emergency situation:

- Contact an alternative vaccine storage facility before packing any vaccine to confirm it can accept vaccines for storage.
- Note any protective measures in place at the time of the event (water bottles, battery-powered TMD, transport to alternative facility, etc.).
- Only open the vaccine storage unit door when ready to pack vaccine in transport containers or when power has been restored.

If an emergency can be anticipated (e.g., weather event), suspend immunization activities before the onset of emergency conditions to allow adequate time for packing and transport.

Storing Vaccines at the Destination

Immediately upon arrival at the off-site location, vaccines should be stored in an appropriate storage unit with a TMD. Follow recommended guidelines for monitoring and recording storage unit temperatures:

- If the device displays minimum/maximum temperatures, this information should be checked and recorded.
- If the device does not display minimum/maximum temperatures, then the current temperature should be checked and recorded a minimum of two times (at the start and end of the workday).

If vaccines cannot be stored in an on-site storage unit, they should be kept in the portable vaccine storage unit using the following guidance:

- Place a TMD (preferably with a probe in a thermal buffer) as close as possible to the vaccines and check and record temperatures hourly.
- Keep the container closed as much as possible.

NOTES

NOTES

Acknowledgements

The editors would like to acknowledge Jennifer Hamborsky, Beth Hibbs, Ginger Redmon, Donna Weaver, A. Patricia Wodi, and Skip Wolfe for their contributions to this chapter.

Selected References

CDC. *General Best Practice Guidelines for Immunization: Best Practices Guidance of the Advisory Committee on Immunization Practices (ACIP)*. www.cdc.gov/vaccines/hcp/acip-recs/general-recs/downloads/general-recs.pdf, Accessed December 27, 2019 and August 12, 2020.

CDC. *Recommendations and Guidelines: Storage and Handling*. www.cdc.gov/vaccines/recs/storage/default.htm.

CDC. *Vaccine Storage and Handling Toolkit*. www.cdc.gov/vaccines/hcp/admin/storage/toolkit/storage-handling-toolkit.pdf.

Food and Drug Administration (FDA). Vaccines Licensed for Use in the United States. www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm093833.htm.

Immunization Action Coalition. Clinic Resources: Storage and Handling. www.immunize.org/clinic/storage-handling.asp.

Vaccine Administration

JoEllen Wolicki, BSN, RN and Elaine Miller, RN, BSN, MPH

This chapter summarizes best practices related to vaccine administration, a key factor in ensuring vaccination is as safe and effective as possible. Administration involves a series of actions: assessing patient vaccination status and determining needed vaccines, screening for contraindications and precautions, educating patients, preparing and administering vaccines properly, and documenting the vaccines administered. Professional standards for medication administration, manufacturer instructions, and organizational policies and procedures should always be followed when applicable.

Staff Training and Education

Policies should be in place to validate health care professionals' knowledge of, and skills in, vaccine administration. All health care professionals should receive comprehensive, competency-based training before administering vaccines. Training, including an observation component, should be integrated into health care professionals' education programs including orientation for new staff and annual continuing education requirements for all staff. In addition, health care professionals should receive educational updates as needed, such as when vaccine administration recommendations are updated or when new vaccines are added to the facility's inventory. Training should also be offered to temporary staff who may be filling in on days when the facility is short-staffed or helping during peak periods of vaccine administration such as influenza season. Once initial training has been completed, accountability checks should be in place to ensure staff follow all vaccine administration policies and procedures.

Before Administering Vaccine

Health care professionals should be knowledgeable about appropriate techniques to prepare and care for patients when administering vaccines.

Assess for Needed Vaccines

The patient's immunization status should be reviewed at every health care visit. Using the patient's immunization history, health care providers should assess for all routinely recommended vaccines as well as any vaccines that are indicated based on existing medical condition(s), occupation, or other risk factors.

To obtain a patient's immunization history, information from immunization information systems (IISs), current and historical medical records, and personal shot record cards may be used. In most cases, health care providers should only accept written,

NOTES

NOTES

dated records as evidence of vaccination; however, self-reported doses of influenza vaccine or pneumococcal polysaccharide vaccine (PPSV23) are acceptable.

Missed opportunities to vaccinate should be avoided. If a documented immunization history is not available, administer the vaccines that are indicated based on the patient's age, medical condition(s), and other risk factors, such as planned travel.

Screen for Contraindications and Precautions

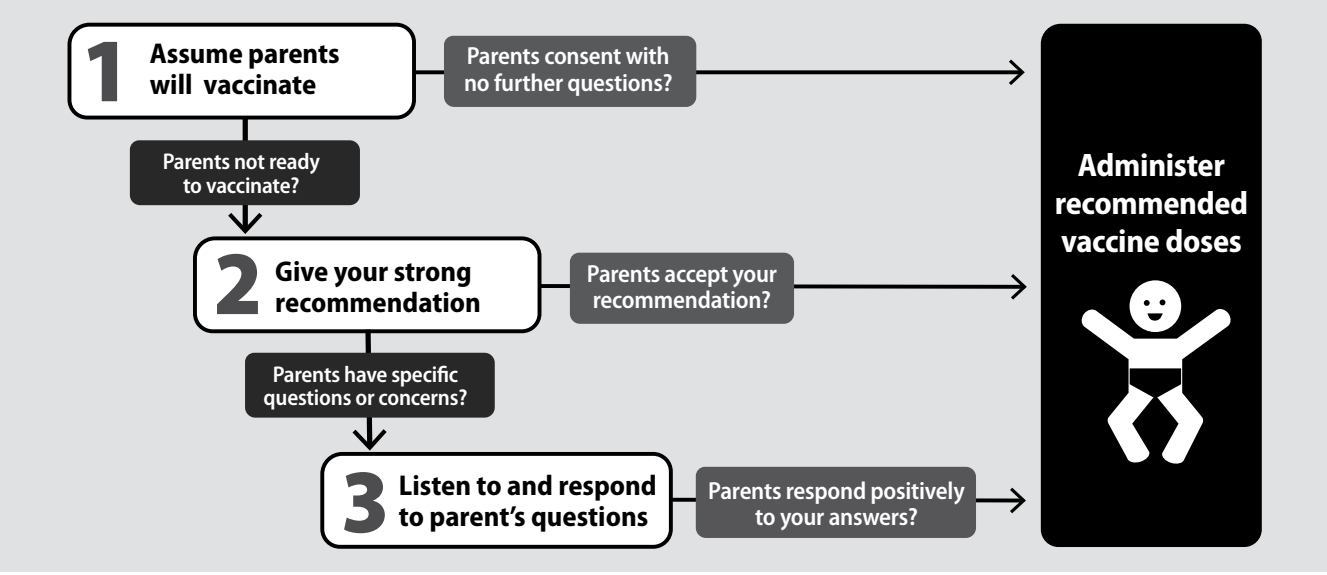
Before administering any vaccine, patients should be screened for contraindications and precautions, even if the patient has previously received that vaccine. The patient's health condition or recommendations regarding contraindications and precautions for vaccination may change from one visit to the next.

To assess patients correctly and consistently, health care providers should use a standardized, comprehensive screening tool. To save time, some facilities ask patients to answer screening questions before seeing the provider, either electronically via an online health care portal or on a paper form while in the waiting or exam room.

Educate Patients or Parents about Needed Vaccines

Vaccines are one of the safest and most effective ways to prevent diseases. All health care personnel, including non-clinical staff, play an important role in promoting vaccination and creating a culture of immunization within a clinical practice. Inconsistent messages from health care personnel about the need for and safety of vaccines may cause confusion about the importance of vaccines.

Talking with Parents about Vaccines for Infants



Studies show health care providers are the most trusted source of vaccine information. Research also shows when a strong recommendation is given by a health care provider, a patient is four to five times more likely to be vaccinated. When providers use presumptive language to initiate vaccine discussions, significantly more parents choose to vaccinate their children, especially at first-time visits. Instead of saying "What do you want to do about shots today," an approach using presumptive language would be to say, "Your child needs three vaccines today."

Some patients and parents may have questions or concerns about vaccination. This does not necessarily mean they will not accept vaccines. Sometimes they simply want to hear their provider's answers to their questions.

Health care professionals need to be prepared to answer questions. In addition, many state and local immunization programs and professional organizations, including the American Academy of Pediatrics, have resources. There are numerous strategies for effectively educating and talking to patients and parents about the need to vaccinate.

Vaccine Information Statements (VISs)

Vaccine information statements (VISs) are documents that inform vaccine recipients or their parents about the benefits and risks of a vaccine. Federal law requires VISs be provided when routinely recommended childhood vaccines are administered. Everyone, including adults, should be given the appropriate VIS when receiving a vaccine covered under the law. The VIS must be given:

- *Before the* vaccine is administered
- *Regardless of the age* of the person being vaccinated (e.g., when influenza vaccine is given to an adult)
- *Every time* a dose of vaccine is administered, even if the patient has received the same vaccine and VIS in the past

CDC encourages the use of *all* VISs, whether the vaccine is covered by the law requiring VIS or not. VISs can be provided at the same time as a screening questionnaire, while the patient is waiting to be seen. They include information that may help the patient or parent respond to the screening questions and can be used by providers during conversations with patients. VISs are available as paper copies and in electronic formats that can be read on smart phones and other devices.

After-Care Instructions

Patient and parent education should also include a discussion of comfort and care strategies after vaccination. After-care instructions should include information for dealing with common side effects such as injection site pain, fever, and

NOTES

NOTES

fussiness (especially in infants). Instructions should also provide information about when to seek medical attention and when to notify the health care provider about concerns that arise following vaccination. After-care information can be given to patients or parents before vaccines are administered, leaving the parent free to comfort the child immediately after the injection. Pain relievers can be used to treat fever and injection-site pain that might occur after vaccination. In children and adolescents, a non-aspirin-containing pain reliever should be used. Aspirin is *not* recommended for children and adolescents.

Vaccine Administration

Infection Control

Health care personnel should follow routine infection control procedures when administering vaccines.

Hand Hygiene

Hand hygiene is critical to prevent the spread of illness and disease. Hand hygiene should be performed before vaccine preparation, between patients, and any time hands become soiled (e.g., when diapering). Hands should be cleansed with a waterless, alcohol-based hand rub or soap and water. When hands are visibly dirty or contaminated with blood or other body fluids, they should be washed thoroughly with soap and water.

Gloves

Occupational Safety and Health Administration (OSHA) regulations have not typically required gloves to be worn when administering vaccines unless the person administering the vaccine is likely to come in contact with potentially infectious body fluids or has open lesions on the hands. In the setting of the COVID-19 pandemic, gloves should be worn when administering intranasal or oral vaccines. If gloves are worn, they should be changed, and hand hygiene should be performed between patients.

Gloves will not prevent needlestick injuries. Any needlestick injury should be reported immediately to the site supervisor, with appropriate care and follow-up given as directed by state and local guidelines.

Vaccine Preparation

Preparing vaccine properly is critical to maintaining the integrity of the vaccine during transfer from the manufacturer's vial to the syringe and, ultimately, to the patient. CDC recommends preparing and drawing up vaccines just before administration. During preparation:

- Follow strict aseptic medication preparation practices.

- Perform hand hygiene *before* preparing vaccines.
- Use a designated, clean medication area that is not adjacent to areas where potentially contaminated items are placed.
- Avoid distractions. Some facilities have a no-interruption zone, where health care professionals can prepare medications without interruptions.
- Prepare medications for *one* patient at a time.
- Always follow the vaccine manufacturer's directions, located in the package inserts.

Choose the Correct Vaccine

Vaccines are available in different presentations, including single-dose vials (SDV), manufacturer-filled syringes (MFS), multidose vials (MDV), oral applicators, and a nasal sprayer. Always check the label on the vial or box to determine:

- It is the correct vaccine and diluent (if needed).
- The expiration date has not passed. Expired vaccine or diluent should never be used.

Single-Dose Vials (SDV)

Most vaccines are available in SDVs. SDVs do not contain preservatives to help prevent microorganism growth. Therefore, vaccines packaged as SDVs are intended to be punctured once for use in *one* patient and for *one* injection. Even if the SDV appears to contain more vaccine than is needed for one patient, it should not be used for more than one patient. Once the appropriate dosage has been withdrawn, the vial and any leftover contents should be discarded appropriately. SDVs with any leftover vaccine should never be saved to combine leftover contents for later use.

Manufacturer-Filled Syringes (MFS)

MFSs are prepared with a single dose of vaccine and sealed under sterile conditions by the manufacturer. Like SDVs, MFSs do not contain a preservative to help prevent the growth of microorganisms. MFSs are intended for one patient for one injection. Once the sterile seal has been broken, the vaccine should be used or discarded by the end of the workday.

Multidose Vials (MDV)

A MDV contains more than one dose of vaccine. MDVs are labeled by the manufacturer and typically contain an antimicrobial preservative to help prevent the growth of microorganisms. Because MDVs contain a preservative, they can be punctured more than once. MDVs used for more than one patient should only be kept and accessed in a dedicated, clean medication preparation area, away from any

NOTES

NOTES

nearby patient treatment areas. This is to prevent inadvertent contamination of the vial through direct or indirect contact with potentially contaminated surfaces or equipment. Only the number of doses indicated in the manufacturer's package insert should be withdrawn from the vial. Partial doses from two or more vials should never be combined to obtain a dose of vaccine.

Oral Applicators and Nasal Sprayer

An oral applicator is for use with oral vaccines and contains only one dose of medication. Oral vaccines do not contain a preservative. Rotavirus vaccine is administered using an oral applicator. An intranasal sprayer is used for the live, attenuated influenza vaccine.

Inspect the Vaccine

Each vaccine and diluent (if needed) should be carefully inspected for damage, particulate matter, or contamination before using. Verify the vaccine has been stored at proper temperatures.

Check the Expiration Date of the Vaccine or Diluent

Determining when a vaccine or diluent expires is an essential step in the vaccine preparation process. The expiration date printed on the vial or box should be checked before preparing the vaccine.

- When the expiration date has only a month and year, the product may be used up to and including the last day of that month unless the vaccine was contaminated or compromised in some way.
- If a day is included with the month and year, the product may only be used through the end of that day unless the vaccine was contaminated or compromised in some way.

Beyond-Use Date (BUD)

In some instances, vaccine must be used by a date earlier than the expiration date on the label. This time frame is referred to as the "beyond-use date" (BUD). The BUD supersedes but should never exceed the manufacturer's expiration date. Vaccines should not be used after the BUD. The BUD should be noted on the label, along with the initials of the person making the calculation. Examples of vaccines with BUDs include:

- Reconstituted vaccines have a limited period for use once the vaccine is mixed with a diluent. This time period is discussed in the package insert.

- Some MDVs vials have a specified period for use once they have been punctured with a needle. For example, the package insert may state the vaccine must be discarded 28 days after it is first punctured.
- Manufacturer-shortened expiration dates may apply when vaccine is exposed to inappropriate storage conditions. The manufacturer might determine the vaccine can still be used but will expire on an earlier date than the date on the label.

Reconstitute Lyophilized Vaccine

Reconstitution is the process of adding a diluent to a dry ingredient to make it a liquid. The lyophilized vaccine (powder or pellet form) and its diluent come together from the manufacturer. Vaccines should be reconstituted according to manufacturer guidelines using only the diluent supplied for a specific vaccine. Diluents vary in volume and composition, and are specifically designed to meet volume, pH balance, and the chemical requirements of their corresponding vaccines. A different diluent, a stock vial of sterile water, or normal saline should never be used to reconstitute vaccines. If the wrong diluent is used, the vaccine dose is not valid and must be repeated using the correct diluent. Vaccine should be reconstituted just before administering by following the instructions in the vaccine package insert.

Once reconstituted, the vaccine should be administered within the time frame specified for use in the manufacturer's package insert; otherwise, the vaccine should be discarded. Changing the needle between preparing and administering the vaccine is not necessary unless the needle is contaminated or damaged.

Choose the Correct Supplies to Administer Vaccines by Injection

OSHA requires that safety-engineered injection devices (e.g., needle-shielding syringes or needle-free injectors) be used for injectable vaccines in all clinical settings to reduce the risk of needlestick injury and disease transmission. General guidance when selecting supplies to administer a vaccine by injection includes:

- Inspect the packaging; never use supplies with torn or compromised packaging.
- Some syringes and needles are packaged with an expiration date. If present, check the expiration date. Never use expired supplies.
- Use a separate syringe and needle for each injection. Never administer a vaccine from the same syringe to more than one patient, even if the needle is changed.

NOTES

Syringe Selection

An injectable vaccine may be administered in either a 1-mL or 3-mL syringe.

Needle Selection

Vaccines must reach the desired tissue to provide an optimal immune response and reduce the likelihood of injection-site reactions. A supply of needles should be available in varying lengths appropriate for the facility's patient population. Clinical judgment should be used when selecting needle length. Needle selection should be based on the:

- Route of administration
- Patient age
- Gender and weight (for adults age 19 years or older)
- Injection site
- Injection technique

Needle Length and Gauge for *Subcutaneous* Injection

Age and Gender	Needle Length and Gauge	Injection Site
All ages and both genders	5/8-inch (16 mm): 23- to 25-gauge	Thigh for infants younger than age 12 months*; upper outer triceps area for persons age 12 months and older

*May be administered into the upper outer triceps area if necessary

Needle Length and Gauge: Children and Adolescents (birth – 18 years) for *Intramuscular* Injection

Age and Gender	Needle Length and Gauge	Injection Site
Neonate, 28 days or younger	5/8-inch (16 mm)*: 22- to 25-gauge	Vastus lateralis muscle of anterolateral thigh
Infants, 1–12 months	1-inch (25 mm): 22- to 25-gauge	Vastus lateralis muscle of anterolateral thigh
Toddlers, 1–2 years	1- to 1.25-inch (25–32 mm): 22- to 25-gauge	Vastus lateralis muscle of anterolateral thigh (preferred site)
	5/8*- to 1-inch (16–25 mm): 22- to 25-gauge	Deltoid muscle of arm
Children, 3–10 years	5/8*- to 1-inch (16–25 mm): 22- to 25-gauge	Deltoid muscle of arm (preferred site)
	1- to 1.25-inch (25–32 mm): 22- to 25-gauge	Vastus lateralis muscle of anterolateral thigh
Children, 11–18 years	5/8*- to 1-inch (16–25mm): 22- to 25-gauge	Deltoid muscle of arm (preferred site)†

*If the skin is stretched tightly and subcutaneous tissues are not bunched.

†The vastus lateralis muscle of the anterolateral thigh can also be used. Most adolescents and adults will require a 1- to 1.5-inch (25–38 mm) needle to ensure intramuscular administration.

Needle Length and Gauge: Adults (age 19 years or older) for *Intramuscular* Injection

Age and Gender	Needle Length and Gauge	Injection Site
Less than 130 lbs (60 kg)	1-inch (25 mm)*: 22- to 25-gauge	Deltoid muscle of arm (preferred site)†
130–152 lbs (60–70 kg)	1-inch (25 mm): 22- to 25-gauge	
Men, 153–260 lbs (70–118 kg)	1- to 1.5-inch (25–38 mm): 22- to 25-gauge	
Women, 153–200 lbs (70–90 kg)	1- to 1.5-inch (25–38 mm): 22- to 25-gauge	
Men, greater than 260 lbs (118 kg)	1.5-inch (38 mm): 22- to 25-gauge	
Women, greater than 200 lbs (90 kg)	1.5-inch (38 mm): 22- to 25-gauge	

*Some experts recommend a 5/8-inch needle for men and women weighing less than 60 kg; if used, skin must be stretched tightly and subcutaneous tissues must not be bunched.

†The vastus lateralis muscle of the anterolateral thigh can also be used. Most adolescents and adults will require a 1- to 1.5-inch (25–38 mm) needle to ensure intramuscular administration.

Filling Syringes

Standard medication preparation guidelines should be followed for drawing a dose of vaccine into a syringe. The cap on the top of an unopened vaccine vial functions as a dust cover. However, not all vaccine manufacturers guarantee the tops of unused vials are sterile, and the way the cover over the stopper is removed can potentially contaminate the stopper. Therefore, using friction and a sterile alcohol swab to wipe the stopper may help assure aseptic technique. Alcohol evaporates quickly and will dry while the needle is being prepared for insertion into the vial.

Instilling air into a multidose vial prior to withdrawing a vaccine dose is not necessary. It could cause a "spritz" of vaccine to be lost the next time the vial is entered, which, over time, can decrease the amount of vaccine in the vial and lead to the loss of a dose (e.g., only nine full doses in a 10-dose vial).

Before withdrawing each dose, the vial should be agitated to mix the vaccine thoroughly and obtain a uniform suspension. The vaccine should be visually inspected for discoloration and precipitation or to see if it cannot be resuspended before administration. If problems are noted, the vaccine should not be administered.

When filling a syringe:

- Never enter a vial with a previously used syringe or needle.
- Never mix different vaccine products in the same syringe.
- Never transfer vaccine from one syringe to another.
- Never combine partial doses from separate vials to obtain a full dose.

NOTES

Once the syringe is filled, label it with the name of the vaccine in the syringe. Often more than one vaccine is administered at the same visit and, once drawn into a syringe, vaccines look similar. By labeling the syringe, health care providers will know the route to use to administer the vaccine correctly.

Predrawing Vaccine

Vaccines should be drawn just before administration. However, while MFSs are recommended for large vaccination clinics, there may be rare instances when the only option is to predraw vaccine for off-site clinics.

Procedural Pain Management

Vaccinations are the most common source of procedural pain for healthy children and can be a stressful experience for persons of any age. It has been estimated that up to 25% of adults have a fear of needles, with most needle fears developing during childhood. If not addressed, these fears can have long-term effects such as preprocedural anxiety and avoidance of needed health care throughout a person's lifetime. Fear of injections and needlestick pain are often cited as reasons why children and adults refuse vaccines.

Pain is a subjective phenomenon influenced by multiple factors, including an individual's age, anxiety level, previous health care experiences, and culture. Although pain from vaccination is to some extent unavoidable, there are some things that parents and health care providers can do to help. Evidence-based pharmacologic, physical, and psychological interventions exist to ease the pain associated with injections. Combining the interventions described below has been shown to improve pain relief.

Inject Vaccines Rapidly Without Aspiration

Aspiration is not recommended before administering a vaccine. Aspiration prior to injection and injecting medication slowly are practices that have not been evaluated scientifically. Aspiration was originally recommended for theoretical safety reasons and injecting medication slowly was thought to decrease pain from sudden distention of muscle tissue. Aspiration can increase pain because of the combined effects of a longer needle-dwelling time in the tissues and shearing action (wiggling) of the needle. There are no reports of any person being injured because of failure to aspirate.

The veins and arteries within reach of a needle in the anatomic areas recommended for vaccination are too small to allow an intravenous push of vaccine without blowing out the vessel. A 2007 study from Canada compared infants' pain response using slow injection, aspiration, and slow withdrawal with another group using rapid injection, no aspiration, and rapid withdrawal. Based on behavioral and visual pain scales, the

group that received the vaccine rapidly without aspiration experienced less pain. No immediate adverse events were reported with either injection technique.

Inject Vaccines that Cause the Most Pain Last

Many persons receive two or more injections at the same clinical visit. Some vaccines cause more pain than others during the injection. Because pain can increase with each injection, the order in which vaccines are injected matters. Some vaccines cause a painful or stinging sensation when injected; examples include measles, mumps, and rubella; pneumococcal conjugate; and human papillomavirus vaccines. Injecting the most painful vaccine last when multiple injections are being administered can decrease the pain associated with the injections.

Breastfeed Children Age 2 Years or Younger During Vaccine Injections

Mothers who are breastfeeding should be encouraged to breastfeed children age 2 years or younger before, during, and after vaccination. Several aspects of breastfeeding are thought to decrease pain by multiple mechanisms: being held by the parent, feeling skin-to-skin contact, suckling, being distracted, and ingesting breast milk. Potential adverse events such as gagging or spitting up have not been reported. Alternatives to breastfeeding include bottle-feeding with expressed breast milk or formula throughout the procedure, which simulates aspects of breastfeeding.

Give a Sweet-Tasting Solution to Children Who Are Not Breastfed

Children (age 2 years or younger) who are not breastfed during vaccination may be given a sweet-tasting solution such as sucrose or glucose one to two minutes before the injection. The analgesic effect can last for up to 10 minutes following administration and can mitigate vaccine injection pain. Parents should be counseled that sweet-tasting liquids should only be used for the management of pain associated with a procedure such as an injection and not as a comfort measure at home.

Pain Relievers

Topical anesthetics block transmission of pain signals from the skin. They decrease the pain as the needle penetrates the skin and reduce the underlying muscle spasm, particularly when more than one injection is administered. These products should be used only for the ages recommended and as directed by the manufacturer. Because using topical anesthetics may require additional time, some planning by the healthcare provider and parent may be needed. Topical anesthetics can be applied during the usual clinic waiting times, or before the patient arrives at the clinic provided parents and patients have been shown how to use them

NOTES

NOTES

appropriately. There is no evidence that topical anesthetics have an adverse effect on the vaccine immune response.

The prophylactic use of antipyretics (e.g., acetaminophen and ibuprofen) before or at the time of vaccination is not recommended. There is no evidence these will decrease the pain associated with an injection. In addition, some studies have suggested these medications might suppress the immune response to some vaccine antigens.

Follow Age-Appropriate Positioning Best Practices

For both children and adults, the best position and type of comforting technique should be determined by considering the patient's age, activity level, safety, comfort, and administration route and site. Parents play an important role when infants and children receive vaccines. Parent participation has been shown to increase a child's comfort and reduce the child's perception of pain. Holding infants during vaccination reduces acute distress. Skin-to-skin contact for infants up to age 1 month has been demonstrated to reduce acute distress during the procedure.

A parent's embrace during vaccination offers several benefits. A comforting hold:

- Avoids frightening children by embracing them rather than overpowering them
- Allows the health care professional steady control of the limb and the injection site
- Prevents children from moving their arms and legs during injections
- Encourages parents to nurture and comfort their child

A combination of interventions, holding during the injection along with patting or rocking after the injection, is recommended for children up to age 3 years. Parents should understand proper positioning and holding for infants and young children. Parents should hold the child in a comfortable position, so that one or more limbs are exposed for injections.

Research shows that children age 3 years or older are less fearful and experience less pain when receiving an injection if they are sitting up rather than lying down. The exact mechanism behind this phenomenon is unknown. It may be that the child's anxiety level is reduced, which, in turn, reduces the child's perception of pain.

Tactile Stimulation

Moderate tactile stimulation (rubbing or stroking the skin) near the injection site before and during the injection process may decrease pain in children age 4 years or older and in adults. The mechanism for this is thought to be that the sensation of touch competes with the feeling of pain from the injection and, thereby, results in less pain.

Route and Site for Vaccination

The recommended route and site for each vaccine are based on clinical trials, practical experience, and theoretical considerations. There are five routes used to administer vaccines. Deviation from the recommended route may reduce vaccine efficacy or increase local adverse reactions. Some vaccine doses are not valid if administered using the wrong route, and revaccination is recommended.

Oral Route (PO)

Oral vaccines should generally be administered before injectable vaccines. Rotavirus vaccines (RV1 [Rotarix], RV5 [RotaTeq]) are administered orally. Because the two brands of rotavirus vaccine are prepared differently and have different types of oral applicators, health care professionals should be familiar with how to prepare and administer the brand stocked in their facility. Rotavirus vaccine should never be injected.

To administer rotavirus vaccine:

- Perform proper hand hygiene. In the setting of the COVID-19 pandemic, gloves should be worn.
- Administer the liquid vaccine slowly against the inside of the infant's cheek (between the cheek and gum) toward the back of the infant's mouth. Never administer the vaccine directly into the throat. This can increase the chance that the infant will cough or gag and spit out the vaccine rather than swallowing it.
- Allow the infant time to swallow.
- Care should be taken to avoid triggering the gag reflex.

An infant can eat or drink immediately before or after administration of either product. The dose does not need to be repeated if an infant regurgitates, spits out the vaccine, or vomits during or after administration. No data exist on the benefits or risks associated with readministering a dose of rotavirus vaccine. The infant should receive the remaining recommended doses of rotavirus vaccine following the routine schedule.

NOTES

NOTES

Intranasal Route (NAS)

Live, attenuated influenza (LAIV [FluMist]) vaccine is administered by the intranasal route. LAIV is administered into each nostril using a manufacturer-filled nasal sprayer. A dose-divider clip, located on the plunger, separates the total vaccine dose of 0.2 mL into two equal parts of 0.1 mL each. LAIV should never be injected. The patient should be seated in an upright position and instructed to breathe normally. The provider should gently place a hand behind the patient's head to prevent inadvertent movement.

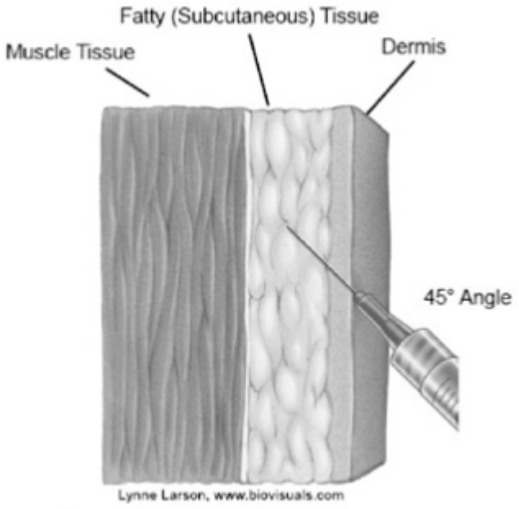
To administer the vaccine:

- Perform proper hand hygiene. In the setting of the COVID-19 pandemic, gloves should be worn.
- Remove the rubber tip of the nasal sprayer and place the tip of the applicator just inside the patient's nostril.
- Push the plunger rapidly in a single motion until the dose-divider clip is reached.
- Pinch and remove the dose-divider clip.
- Place the tip of the applicator just inside the other nostril and repeat the process to administer the remaining vaccine.

The dose does not need to be repeated if the patient coughs, sneezes, or expels the dose in any other way.

Subcutaneous Route (Subcut)

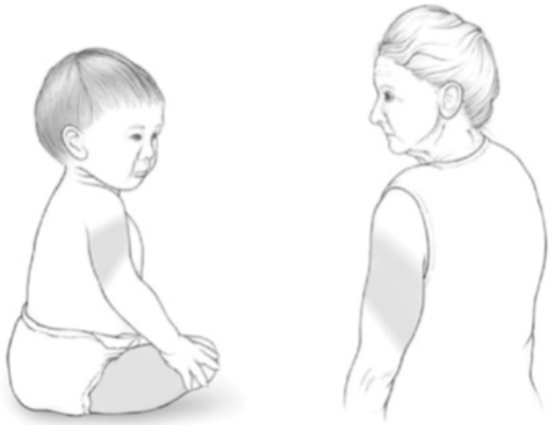
Routinely recommended vaccines administered by subcutaneous injection include MMR (MMR-II), VAR (Varivax), IPV (IPOL), MMRV (ProQuad), and PPSV23 (Pneumovax 23). IPOL and Pneumovax 23 can be administered by intramuscular (IM) or subcutaneous injection.



Subcutaneous injections are administered into the fatty tissue found below the dermis and above muscle tissue. For infants younger than age 12 months, a subcutaneous injection

is usually administered into the fatty tissue of the thigh, although the upper outer triceps area of the arm may be used if necessary. For persons age 1 year or older, subcutaneous injections are given in the fatty tissue above the upper outer triceps of the arm.

Sites for Subcutaneous Injection

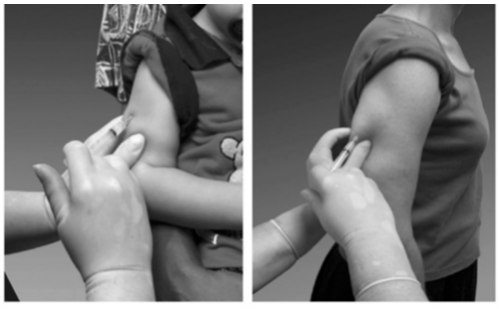


Source: California Department of Public Health

When administering a vaccine subcutaneously:

- Perform proper hand hygiene.
- Cleanse the skin with a sterile alcohol swab and allow it to dry.
- Pinch up the skin and underlying fatty tissue.
- Insert the needle at a 45-degree angle into the subcutaneous tissue and inject the vaccine. Avoid reaching the muscle.
- Withdraw the needle.
- Apply an adhesive bandage to the injection site if there is any bleeding.

Subcutaneous Administration Technique



Source: California Department of Public Health

Intradermal Injection

No routinely recommend U.S. vaccines are administered by the intradermal route of injection.

NOTES

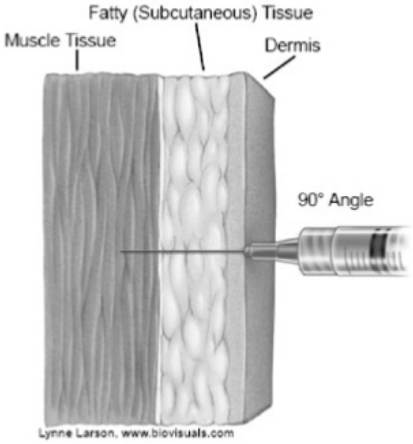
NOTES

Intramuscular Route

Routinely recommended vaccines administered by IM injection include:

- DT
- DTaP (Daptacel, Infanrix)
- DTaP-IPV-HepB (Pediarix)
- DTaP-IPV/Hib (Pentacel)
- DTaP-IPV (Kinrix, Quadracel)
- Hib (PedvaxHIB, ActHIB, Hiberix)
- HepA (Havrix, Vaqta)
- HepB (Engerix B, Recombivax HB)
- HepB-CpG (Heplisav-B)
- HepA-HepB (Twinrix)
- HPV (Gardasil 9)
- IIV (multiple brands)
- IPV (IPOL)
- MenACWY (Menactra, MenQuadfi, Menveo)
- MenB (Bexsero, Trumenba)
- PCV13 (Prevnar 13)
- PPSV23 (Pneumovax 23)
- RZV (Shingrix)
- Td (Tenivac, Tdvax)
- Tdap (Adacel, Boostrix)

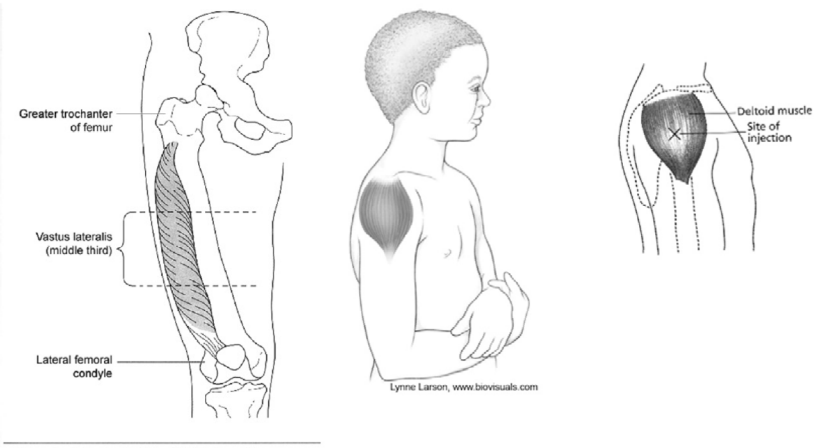
IPOL and Pneumovax 23 can be administered by IM or subcut injection



IM injections are administered into the muscle through the skin and subcutaneous tissue. There are only two recommended sites for administering vaccines by IM injection:

- Vastus lateralis muscle in the anterolateral thigh
- Deltoid muscle in the upper arm

Sites for Intramuscular Injection



The vastus lateralis site of the right thigh, used for an intramuscular injection.

Source: Lynne Larson, www.biovisuals.com

Injection at these sites reduces the chance of involving neural or vascular structures. The preferred site depends on the patient's age, weight, gender, and the degree of muscle development.

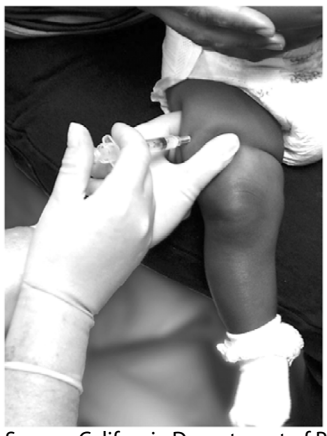
When administering an IM injection:

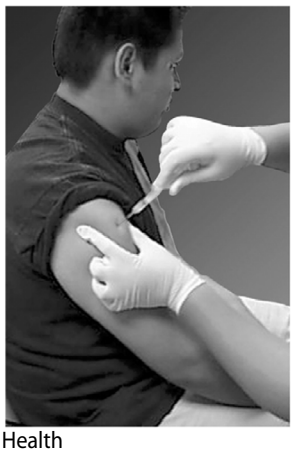
- Perform proper hand hygiene.
- Identify the appropriate landmarks for the site.
- Cleanse the skin with a sterile alcohol swab and allow it to dry.
- Spread the skin tight to isolate the muscle. Another acceptable technique for pediatric and geriatric patients is to grasp the tissue and "bunch up" the muscle.
- Insert the needle at a 90-degree angle and inject the vaccine.
- Withdraw the needle.
- Apply an adhesive bandage to the injection site if there is any bleeding.

NOTES

NOTES

Intramuscular Administration Technique





Source: California Department of Public Health

Site Recommendations for Intramuscular Vaccination

For both sites, an IM injection ideally should be administered into the middle of the muscle where the muscle tissue is thickest.

Infants (12 Months or Younger)

For most infants, the vastus lateralis muscle in the anterolateral thigh is the recommended site for injection because it provides a large muscle mass. The muscles of the buttock are not used for administration of vaccines in infants and children because of concern about potential injury to the sciatic nerve, which has been well-documented after injection of antimicrobial agents into the buttock. If the gluteal muscle must be used (e.g., because of reduced anatomic site availability), care should be taken to define the anatomic landmarks. A gluteal muscle injection should be administered laterally and superior to a line between the posterior superior iliac spine and the greater trochanter or in the ventrogluteal site, the center of a triangle bound by the anterior superior iliac spine, the tubercle of the iliac crest, and the upper border of the greater trochanter.

Toddlers (1 Year through 2 Years)

For toddlers, the vastus lateralis muscle in the anterolateral thigh is preferred. The deltoid muscle can be used if the muscle mass is adequate.

Children/Adolescents (3 Years through 18 Years)

The deltoid muscle is preferred for children age 3 through 18 years. The vastus lateralis muscle in the anterolateral thigh is an alternative site if the deltoid sites cannot be used.

Adults (19 Years or Older)

For adults, the deltoid muscle is recommended. IM injections are administered at a 90-degree angle to the skin and, for most adult patients, the skin is spread and the tissues are not

bunched. It is acceptable in geriatric patients to grasp the tissue and "bunch up" the muscle. As with children and adolescents, the vastus lateralis muscle in the anterolateral thigh is an alternative site if the deltoid sites cannot be used.

Multiple Vaccinations

Children and adults often need more than one vaccine at the same time. Giving more than one vaccine at the same clinical visit is preferred because it helps keep patients up-to-date. Use of combination vaccines can reduce the number of injections. Considerations when administering multiple injections include:

- Administer each vaccine in a different injection site. Recommended sites (i.e., vastus lateralis and deltoid muscles) have multiple injection sites. Separate injection sites by 1 inch or more, if possible, so that any local reactions can be differentiated.
- For infants and younger children, if more than two vaccines are being injected into the same limb, the thigh is the preferred site because of the greater muscle mass. For older children and adults, the deltoid muscle can be used for more than one intramuscular injection.
- Vaccines that are the most reactive and more likely to cause an enhanced injection site reaction (e.g., DTaP, PCV13) should be administered in different limbs, if possible.
- Vaccines that are known to be painful when injected (e.g., HPV, MMR) should be administered after other vaccines.
- If both a vaccine and an immune globulin (Ig) preparation are needed (e.g., Td/Tdap and tetanus immune globulin [TIG] or hepatitis B vaccine and hepatitis B immune globulin [HBIG]), administer the vaccine in a separate limb from the immune globulin.

Vaccine and Supply Disposal

Immediately after use, all syringe/needle devices should be placed in biohazard containers that are closable, puncture-resistant, leakproof on sides and bottom, and labeled or color-coded. This practice helps prevent accidental needlestick injury and reuse. Used needles should not be recapped or cut or detached from the syringes before disposal.

Empty or expired vaccine vials are considered medical waste and should be disposed of according to state regulations.

Medical waste disposal requirements are set by state environmental agencies. Contact the state or local immunization program or state environmental agency for guidance.

NOTES

NOTES

Patient Care after Vaccine Administration

Health care providers should be knowledgeable about the policies and procedures for identifying and reporting adverse events after vaccination. A vaccine adverse event refers to any medical event that occurs after vaccination which may or may not be related to vaccination. Further assessment is needed to determine if an adverse event is caused by a vaccine. An adverse vaccine reaction is an untoward effect caused by a vaccine.

Managing Acute Reactions after Vaccination

Health care providers should be familiar with strategies to prevent and identify adverse reactions after vaccination. Potential life-threatening adverse reactions that can occur immediately after vaccination are severe allergic reactions and syncope (fainting).

Severe Allergic Reactions

Severe, life-threatening anaphylactic reactions following vaccination are rare. Thorough screening for contraindications and precautions prior to vaccination can often prevent reactions. Health care providers should be familiar with identifying immediate-type allergic reactions. Symptoms of immediate-type allergic reactions can include local or generalized urticaria (hives), angioedema, respiratory compromise due to wheezing or swelling of the throat, hypotension, and shock. Health care providers should be competent in treating these events at the time of vaccine administration. All vaccine providers should be certified in cardiopulmonary resuscitation (CPR) and be skilled in administering epinephrine. Equipment needed for maintaining an airway should be available for immediate use and the provider should be skilled in using the equipment. Providers should also have a plan in place to contact emergency medical services immediately if there is an anaphylactic reaction to vaccination, and staff members should know their individual roles in the event of an emergency.

Syncope

All health care professionals who administer vaccines to older children, adolescents, and adults should be aware of the potential for syncope after vaccination and the related risk of injury caused by falls. Appropriate measures should be taken to prevent injuries if a patient becomes weak or dizzy or loses consciousness, including:

- Have the patient seated or lying down for vaccination.
- Be aware of symptoms that precede fainting (e.g., weakness, dizziness, pallor).

- Provide supportive care and take appropriate measures to prevent injuries if such symptoms occur.
- Strongly consider observing patients (seated or lying down) for 15 minutes after vaccination to decrease the risk for injury should they faint.

Reporting an Adverse Event

Health care providers are required by law to report certain adverse events, and encouraged to report other events, following vaccination to the Vaccine Adverse Event Reporting System (VAERS). Details on reporting adverse events after vaccination can be found at https://vaers.hhs.gov.

Documenting Vaccinations

Accurate and timely documentation can help prevent administration errors and curtail the number and cost of excess vaccine doses. In addition, preventing excess doses of vaccines may decrease the number of adverse reactions. All vaccines administered should be fully documented in the patient's permanent medical record. Health care providers who administer vaccines covered by the National Vaccine Injury Compensation Program (which include all vaccines listed on the Advisory Committee on Immunization Practices recommended child and adolescent immunization schedule) are required by law to ensure the permanent medical record of the recipient indicates:

- Date of administration
- Vaccine manufacturer
- Vaccine lot number
- Name and title of the person who administered the vaccine and the address of the facility where the permanent record will reside
- The edition date of the VIS distributed and the date it was provided to the patient

Vaccine administration best practices also include documenting the route, dosage, and site. Providers should update a patient's permanent medical record to reflect any documented episodes of adverse events after vaccination and any serologic test results related to vaccine-preventable diseases (e.g., those for rubella screening or antibody to hepatitis B surface antigen). The patient or parent should be provided with a personal immunization record that includes the vaccination(s) and date administered.

Although there is no national law, it is also important to document when parents or adult patients refuse vaccines despite the vaccine provider's recommendation. Professional

NOTES

NOTES

organizations such as the American Academy of Pediatrics and others have developed forms to document when vaccines are refused (https://www.aap.org/en-us/documents/immunization_refusaltovaccinate.pdf).

By age 2 years, more than 20% of the children in the United States typically have seen more than one health care provider, resulting in scattered paper medical records. IISs are confidential, population-based, computerized information systems that collect and consolidate vaccination data from multiple health care providers. Vaccine providers are strongly encouraged to participate in an IIS, and some states mandate documenting vaccinations in an IIS. Laws regarding using an IIS vary by state or region.

Some states' IISs use bar-coding technology. Implementation of a 2D bar code on vaccine vials and VISs allows for rapid, accurate, and automatic capture of certain data, including the vaccine product identifier, lot number, expiration date, and VIS edition date using a handheld imaging device or scanner that could populate these fields in an IIS and/or an electronic health record.

Vaccine Administration Errors

The National Coordinating Council for Medication Error Reporting and Prevention defines a medication error as "any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer." A *preventable event* is one that is due to an error that could be avoided. For example, if a patient receives the wrong drug because of look-alike labels between different products, that is considered a preventable event. Vaccines, like other medications, can be involved in errors. Vaccine administration errors can have many consequences, including inadequate immunological protection, possible injury to the patient, cost, inconvenience, and reduced confidence in the health care delivery system.

Common vaccine administration errors include:

- Doses administered too early (e.g., before the minimum age or interval)
- Wrong vaccine (e.g., Tdap instead of DTaP)
- Wrong dosage (e.g., pediatric formulation of hepatitis B vaccine administered to an adult)
- Wrong route (e.g., MMR given by IM injection)
- Vaccine administered outside the approved age range
- Expired vaccine or diluent administered
- Improperly stored vaccine administered

- Vaccine administered to a patient with a contraindication
- Wrong diluent used to reconstitute the vaccine or only the diluent was administered

Traditionally, medication errors are thought to be caused by mistakes. This "blame-seeking" approach fails to address the root cause, potentially causing the error to recur. An environment that values the reporting and investigation of errors (and "near misses") as part of risk management and quality improvement should be established. Health care personnel should be encouraged to report errors and trust that the situation and those involved will be treated fairly without fear of punishment and ridicule. Error reporting provides opportunities to discover how the errors occur and to share ideas to prevent or reduce those errors in the future. When a vaccine administration error occurs, health care providers should determine how it happened and put strategies in place to prevent it in the future.

Guidance for handling some common vaccine administration errors is included in ACIP's *General Best Practice Guidelines for Immunization*. Some vaccine administration errors require revaccination, but others do not.

Vaccine administration errors requiring revaccination include:

- Hepatitis B vaccine administered by any route other than IM injection, or in adults at any site other than the deltoid or anterolateral thigh
- HPV vaccine that is administered by any route other than IM injection
- Influenza vaccine administered subcutaneously
- Any vaccination using less than the appropriate dose (e.g., pediatric formulation hepatitis A vaccine given to an adult) does not count and the dose should be repeated according to age unless serologic testing indicates an adequate response has developed (however, if two half-volume formulations of vaccine are administered on the same clinic day, these 2 doses can count as 1 valid dose)
- If a partial dose of an injectable vaccine is administered because the syringe or needle leaks or the patient jerks away

Vaccine administration errors not requiring revaccination include:

- Any vaccination using more than the appropriate dose (e.g., DTaP administered to an adult) should be counted if the minimum age and minimum interval have been met.

NOTES

NOTES

- Hepatitis A vaccine and meningococcal conjugate vaccine administered by the subcutaneous route if the minimum age and minimal interval have been met
- Administering a dose 4 or fewer days earlier than the minimum interval or age is unlikely to have a substantially negative effect on the immune response to that dose. Vaccine doses administered in this 4-day grace period before the minimum interval or age, with a few exceptions, are considered valid. However, state or local mandates might supersede this guideline.
- MMR, varicella, and MMRV administered by IM injection if the minimum age and minimum interval have been met

Acknowledgements

The editors would like to acknowledge Beth Hibbs and Andrew Kroger for their contributions to this chapter.

Selected References

Australian Technical Advisory Group on Immunization (ATAGI). *Australian Immunization Handbook, Australian Government Department of Health*. Canberra; 2018. https://immunisationhandbook.health.gov.au/. Accessed October 11, 2020.

Canadian Government. Public Health Agency of Canada. *Canadian Immunization Guide*. www.canada.ca/en/public-health/services/canadian-immunization-guide.html. Accessed October 11, 2020.

CDC. *General Best Practice Guidelines for Immunization: Best Practices Guidance of the Advisory Committee on Immunization Practices (ACIP)*. www.cdc.gov/vaccines/hcp/acip-recs/general-recs/index.html. Accessed October 11, 2020.

CDC. *Injection Safety*. www.cdc.gov/injectionsafety/index.html. Accessed October 11, 2020.

Cohen M. *Medication Errors*. 2nd ed. Washington, D.C.: American Pharmacists Association;2007.

Committee on Identifying and Preventing Medication Errors. Board of Health Care Services: Aspden P, Wolcott J, Bootman J et al., eds. *Preventing Medication Errors*. Washington D.C.: National Academies of Sciences;2007.

Harrington J, Logan S, Harwell C, et al. Effective analgesia using physical interventions for infant immunizations. *Pediatrics* 2012;129(5):815–22.

Hibbs B, Miller E, Shi J, et al. Safety of vaccines that have been kept outside of recommended temperatures: Reports to the Vaccine Adverse Event Reporting System (VAERS), 2008-2012. *Vaccine* 2018;36(4):553–8.

Hibbs B, Miller E, Shimabukuro T. Centers for Disease Control and Prevention (CDC). Notes from the field: rotavirus vaccine administration errors--United States, 2006-2013. *MMWR* 2014;63(4):81.

Ipp M, Taddio A, Sam J, et al. Vaccine-related pain: randomized controlled trial of two injection techniques. *Arch Dis Child* 2007;92(12):1105–8.

NOTES

NOTES

Jacobson R, St Sauver J, Griffin J, et al. How health care providers should address vaccine hesitancy in the clinical setting: Evidence for presumptive language in making a strong recommendation. *Hum Vaccin Immunother* 2020;16(9):2131–5.

Lynn, P. *Clinical Nursing Skills: A Nursing Process Approach*. 5th ed. Philadelphia PA: Wolters Kluwer;2019.

Moro P, Arana J, Marquez P, et al. Is there any harm in administering extra-doses of vaccine to a person? Excess doses of vaccine reported to the Vaccine Adverse Event Reporting System (VAERS), 2007-2017. *Vaccine* 2019;37(28):3730–4.

Occupational Health and Safety Administration. Occupational exposure to bloodborne pathogens: needlesticks and other sharps injuries: Final Rule (29 CFR Part 1910). *Fed Regist* 2001;66(12):5317–25.

Opel D, Robinson J, Spielvogle H, et al. Presumptively Initiating Vaccines and Optimizing Talk with Motivational Interviewing' (PIVOT with MI) trial: a protocol for a cluster randomised controlled trial of a clinician vaccine communication intervention. *BMJ Open* 2020;10(8):e039299.

Shimabukuro T, Miller E, Strikas R, et al. Notes from the Field: Vaccine Administration Errors Involving Recombinant Zoster Vaccine - United States, 2017-2018. *MMWR* 2018;67(20):585–6.

Smith S, Duell D, Martin, B. *Clinical Nursing Skills: Basic to Advanced Skills*. 8th ed. Saddle River, NJ: Pearson Education, Inc.;2011.

Su J, Miller E, Duffy J, et al. Notes from the Field: Administration Error Involving a Meningococcal Conjugate Vaccine-- United States, March 1, 2010-September 22, 2015. *MMWR* 2016;65(6):161–2.

Suragh T, Hibbs B, Marquez P, et al. Age inappropriate influenza vaccination in infants less than 6 months old, 2010-2018. *Vaccine* 2020;38(21):3747–51.

Taddio A, Appleton M, Bortolussi R, et al. Reducing the pain of childhood vaccination: an evidence-based clinical practice guideline. *Can Med Assc Journal* 2010;182:1989–95.

Taddio A, Ilersich A, Ipp M, et al. Physical interventions and injection techniques for reducing injection pain during routine childhood immunizations systematic review of randomized controlled trials and quasi-randomized controlled trials. *Clinical Therapeutics* 2009;31(Suppl 2):S48–S76.

Taddio A, McMurtry C, Shah V, et al. Reducing pain during vaccine injections: clinical practice guideline. *CMAJ* 2015;187(13):975–82.

Taylor L, Greeley R, Dinitz-Sklar I, et al. Notes from the Field: Injection Safety and Vaccine Administration Errors at an Employee Influenza Vaccination Clinic—New Jersey, 2015. *MMWR* 2015;64(49):1363–4.

NOTES

Vaccine Administration

6

Anna M. Acosta, MD; Pedro L. Moro, MD, MPH; Susan Hariri, PhD; and Tejpratap S.P. Tiwari, MD

Diphtheria is an acute, bacterial disease caused by toxin-producing strains of *Corynebacterium diphtheriae*. The name of the disease is derived from the Greek diphthera, meaning 'leather hide.' The disease was described in the 5th century BCE by Hippocrates, and epidemics were described in the 6th century AD by Aetius. The bacterium was first observed in diphtheritic membranes by Edwin Klebs in 1883 and cultivated by Friedrich Löffler in 1884. Beginning in the early 1900s, prophylaxis was attempted with combinations of toxin and antitoxin. Diphtheria toxoid was developed in the early 1920s 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

- Described by Hippocrates in 5th century BCE
- Epidemics described in 6th century
- Bacterium first observed in 1883 and cultivated in 1884
- Diphtheria 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 specific viruses (corynebacteriophages) carrying the genetic information for the toxin (*tox* gene). Diphtheria toxin causes the local and systemic manifestations of diphtheria.

C. diphtheriae has four biotypes: gravis, intermedius, mitis, and belfanti. All biotypes can become toxigenic and cause severe disease. All isolates of *C. diphtheriae* should be tested for toxigenicity.

Corynebacterium diphtheria

- Aerobic gram-positive bacillus
- Toxin production occurs when bacillus is infected by corynebacteriophages carrying t*ox* gene
- Four biotypes: gravis, intermedius, mitis, and belfanti
- All isolates should be tested for toxigenicity

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 formation of the pseudomembrane that is characteristic of this disease. 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 major complications such as myocarditis, polyneuropathies, and nephritis, and can also cause thrombocytopenia.

Non-toxin-producing *C. diphtheriae* strains can cause mild to severe exudative pharyngitis. Severe cases with pseudomembranes caused by such strains have been reported rarely; it is possible that these infections were caused by toxigenic strains that were not detected because of inadequate culture sampling. Other manifestations of nontoxigenic *C. diphtheriae* infection include cutaneous lesions, endocarditis, bacteremia, and septic arthritis.

Diphtheria Pathogenesis

- Toxigenic diphtheria bacilli acquired in the nasopharynx
  - Produces a toxin that inhibits cellular protein synthesis, destroys local tissue, and forms a pseudomembrane
  - Responsible for major complications, including: myocarditis, polyneuropathies, nephritis, and thrombocytopenia
- Non-toxin-producing *C. diphtheriae* strains cause mild to severe exudative pharyngitis and sometimes lesions, endocarditis, bacteremia, and septic arthritis

Diphtheria Clinical Features

- Incubation period 2 to 5 days (range, 1 to 10 days)
- May involve any mucous membrane
- Classified based on site of disease
  - Respiratory (pharyngeal, tonsillar, laryngeal, nasal)
  - Non-respiratory (cutaneous and other mucus membranes)
- Most common sites of infection are the pharynx and tonsils

Clinical Features

The incubation period for diphtheria is 2 to 5 days, with a range of 1 to 10 days. Disease can involve almost any mucous membrane. In untreated people, organisms can be present in discharges and lesions 2 to 6 weeks after infection. For clinical purposes, it is convenient to classify diphtheria by anatomic site: respiratory (pharyngeal, tonsillar, laryngeal, nasal) and non-respiratory (cutaneous and other mucus membranes) disease.

Pharyngeal and Tonsillar Diphtheria

The most common sites of diphtheria infection are the pharynx and the tonsils. Infection at these sites is usually associated with substantial systemic absorption of toxin. The onset of pharyngitis is gradual. Early symptoms include malaise, sore throat, anorexia, and low-grade fever (less than 101°F). Within 2 to 3 days, a bluish-white membrane forms and extends, varying in size from covering a small patch on the tonsils to covering most of the soft palate. Often by the time a physician is contacted the membrane is greyish-green or, if bleeding has occurred, black. There is a minimal amount of mucosal erythema surrounding the membrane. The membrane is firmly adherent to the tissue, and forcible attempts to remove it cause bleeding. Extensive membrane formation may result in respiratory obstruction.

While some patients may recover at this point without treatment, others may develop severe disease. The patient may appear quite toxic, but the fever is usually not high. Patients with severe disease may develop marked edema of the submandibular areas and the anterior neck along with lymphadenopathy, giving a characteristic "bull neck" appearance. If enough toxin is absorbed, the patient can develop severe prostration, pallor, rapid pulse, stupor, and coma. Death can occur within 6 to 10 days.

Laryngeal Diphtheria

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

Anterior Nasal Diphtheria

The onset of anterior nasal diphtheria looks much like the common cold and is usually characterized by a mucopurulent nasal discharge that 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 from this location, and it can be terminated rapidly by diphtheria antitoxin and antibiotic therapy.

Cutaneous Diphtheria

Skin infections may be manifested by a scaling rash or by ulcers with clearly demarcated edges and an overlying membrane, but any chronic skin lesion may harbor *C. diphtheriae* along with other organisms. Cutaneous diphtheria is quite common in the tropics and is probably responsible for the high levels of natural immunity found in these populations. Infection with toxigenic strains appears to result less frequently in systemic complications with cutaneous compared to other forms of diphtheria. *C. diphtheriae* isolated from cutaneous cases in the United States typically has been nontoxigenic, although recently a number of imported toxigenic cutaneous cases have been identified.

Other

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

Complications

Most complications of diphtheria, including death, are caused by 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. Myocarditis can lead to heart failure and, if it occurs early, it is often fatal.

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

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

The estimated overall case fatality ratio for diphtheria is 5% to 10%.

Diphtheria Complications

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

Laboratory Testing

Diagnosis of respiratory diphtheria is usually made based on clinical presentation because it is imperative to begin presumptive therapy quickly. Non-respiratory diphtheria, such as cutaneous diphtheria, may not be clinically suspected and therefore diagnosis is typically based on the laboratory finding.

Confirmatory testing for diphtheria includes culture to identify the bacterial species and the Elek test to confirm diphtheria toxin production. Capacity for diphtheria culture may be available at public health or commercial laboratories. CDC's Pertussis and Diphtheria Laboratory routinely performs culture to confirm *C. diphtheriae* and is currently the only laboratory in the United States that tests for toxin production. It is critical to take a swab of the affected area, especially any ulcerations or pseudomembranes. The organism can be cultured on common laboratory media; culture on a selective medium containing tellurite allows for distinguishing *C. diphtheriae* and *C. ulcerans* from other Corynebacterium species that normally inhabit the nasopharynx and skin (e.g., diphtheroids). However, further biochemical tests are required to fully identify an isolate as C. *diphtheriae*. If *C. diphtheriae* or C. *ulcerans* are isolated, they must be tested for toxin production.

If antibiotic therapy was started prior to specimen collection from a suspected diphtheria case, and culture was negative for *C. diphtheriae*, two sources of evidence can help support presumptive diagnosis:

1. a positive polymerase chain reaction (PCR) test for diphtheria *tox* gene;
2. isolation of *C. diphtheriae* from cultures of specimens from close contacts.

Medical Management

Diphtheria Antitoxin

Diphtheria antitoxin, produced in horses, has been used for treatment of respiratory diphtheria in the United States since the 1890s. It typically is not administered in cases of non-respiratory diphtheria and it is not indicated for prophylaxis of diphtheria patient contacts. Diphtheria antitoxin is available only from CDC, through an Investigational New Drug (IND) protocol. Diphtheria antitoxin does not neutralize toxin that is already fixed to tissues, but it will neutralize circulating toxin and prevent progression of disease.

After a provisional clinical diagnosis of respiratory diphtheria is made, appropriate specimens should be obtained for culture and the patient placed in isolation. Persons with suspected diphtheria should be promptly given diphtheria antitoxin and antibiotics in adequate dosage, without waiting for laboratory confirmation. Respiratory support and airway maintenance should also be provided as needed. Consultation on the use of and access to diphtheria antitoxin is available through the duty officer at CDC's Emergency Operations Center at 770-488-7100.

Antibiotics

In addition to diphtheria antitoxin, patients with respiratory diphtheria should also be treated with antibiotics. The disease is usually no longer contagious 48 hours after antibiotics have

been given. Elimination of the organism should be documented by two consecutive negative cultures taken 24 hours apart, with the first specimen collected 24 hours after therapy is completed.

Preventive Measures

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

Vaccination history of close contacts of diphtheria patients should also be assessed: if vaccination history is incomplete or unknown, the contact should receive a dose of diphtheria toxoid-containing vaccine immediately, and the vaccination series should be completed according recommendations from the Advisory Committee on Immunization Practices (ACIP). If the contact is up-to-date according to ACIP recommendations but the last dose was more than 5 years ago, a diphtheria toxoid-containing vaccine should be immediately administered. In addition, close contacts should receive a single intramuscular dose of benzathine penicillin G or a 7- to 10-day course of oral erythromycin. Benzathine penicillin G should be given to contacts for whom surveillance cannot be maintained for 7 to 10 days. Contacts should be closely monitored and begin diphtheria antitoxin treatment at the first signs of illness.

Epidemiology

Occurrence

Diphtheria occurs worldwide, particularly in countries with suboptimal vaccination coverage. Diphtheria is rare in industrialized countries, including the United States. Because it is a rare disease, seasonal and geographic distribution patterns are no longer observed.

Reservoir

Humans are the reservoir for *C. diphtheriae*.

Transmission

Transmission is most often person-to-person through respiratory droplets. Transmission may also occur from exposure to infected skin lesions or articles soiled with discharges from these lesions.

Temporal Pattern

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

Diphtheria Epidemiology

- Reservoir
  - Human
- Transmission
  - Person-to-person through respiratory droplets
  - Exposure to infected skin lesions and fomites
- Temporal pattern
  - Winter and spring in temperate climates
- Communicability
  - As long as virulent bacilli are present in discharge and lesions

Communicability

Transmission may occur as long as virulent bacilli are present in discharges and lesions. Effective antibiotic therapy promptly terminates shedding.

Diphtheria Secular Trends in the United States

- 100,000-200,000 cases and 13,000-15,000 deaths reported annually during 1920s before vaccine
- Cases gradually declined after vaccines introduced in 1940s; cases rapidly declined after universal vaccination program introduction in late 1940s
- From 1996 to 2018, 14 cases and 1 death reported in the United States

Secular Trends in the United States

During the 1920s, 100,000 to 200,000 cases of diphtheria (140 to 150 cases per 100,000 population) and 13,000 to 15,000 deaths were reported each year. After diphtheria toxoid-containing vaccines became available in the 1940s, the number of cases gradually declined to about 19,000 in 1945 (15 cases per 100,000 population). A more rapid decrease began with implementation of a universal childhood vaccination program which included diphtheria toxoid-containing vaccines beginning in the late 1940s.

From 1996 through 2018, 14 cases of diphtheria were reported in the United States, an average of less than 1 per year. One fatal case occurred in a 63-year-old male returning to the United States from a country with endemic diphtheria disease.

Within the United States, coverage with diphtheria toxoid childhood vaccines (DTaP) has been consistently high. Among children born during 2016–2017, 93.3% had received at least 3 doses of DTaP vaccine by age 24 months, and 80.6% had received at least 4 doses of DTaP vaccine by age 24 months. Coverage with the adolescent and adult diphtheria toxoid vaccines (Tdap or Td) is variable: Tdap coverage among adolescents age 13 through 17 years reached 90.2% in 2019.

Diphtheria Toxoid-containing Vaccines

- DT
- DTaP (Daptacel and Infanrix)
- Td (Tdvax and Tenivac)
- Tdap (Adacel and Boostrix)
- DTaP-HepB-IPV (Pediarix)
- DTaP-IPV/Hib (Pentacel)
- DTaP-IPV (Kinrix and Quadracel)
- DTaP-IPV-Hib-HepB (Vaxelis)

Diphtheria Toxoid-containing Vaccines

Diphtheria toxoid is produced by growing toxigenic *C. diphtheriae* in liquid medium.

Diphtheria toxoid is combined with tetanus toxoid as diphtheria and tetanus toxoid (DT) vaccine or tetanus and diphtheria toxoid (Td [Tenivac and Tdvax]) vaccine. Diphtheria toxoid is also combined with both tetanus toxoid and acellular pertussis vaccine as DTaP (Infanrix and Daptacel) or Tdap (Boostrix and Adacel) vaccines. Td contains reduced amounts of diphtheria toxoid compared with DT. DTaP and Tdap contain the same pertussis components, but Tdap contains a reduced quantity of some pertussis antigens and diphtheria toxoid. Boostrix contains a reduced quantity of tetanus toxoid compared to Infanrix.

Children younger than age 7 years should receive DTaP vaccine or DT vaccine (in instances where the pertussis vaccine component is contraindicated or where the physician decides that pertussis vaccine is not to be administered). Persons age

7 years or older should receive the Td vaccine or Tdap vaccine, even if they have not completed a series of DTaP or DT (Tdap would be off-label for children age 7 through 9 years but is still recommended by ACIP). Tdap (Boostrix) is approved for persons age 10 years or older; Tdap (Adacel) is approved for persons age 10 through 64 years. DTP vaccines are combined diphtheria and tetanus toxoids and whole cell pertussis vaccine, but none are currently licensed in the United States.

There are five combination vaccines that contain DTaP vaccine. DTaP-HepB-IPV (Pediarix) is licensed for the first 3 doses of the DTaP series among children age 6 weeks through 6 years. DTaP-IPV/Hib (Pentacel) is licensed for the first 4 doses of the component vaccines among children age 6 weeks through 4 years. DTaP-IPV (Kinrix) is licensed only for the fifth dose of DTaP and fourth dose of IPV among children age 4 through 6 years. DTaP-IPV (Quadracel) is licensed only for the fourth dose of DTaP and fourth or fifth dose of IPV among children age 4 through 6 years. DTaP-IPV-Hib-HepB (Vaxelis) is licensed for use in children age 6 weeks through 4 years.

Characteristics

Diphtheria toxoid-containing vaccines are administered by intramuscular injection. Each dose of diphtheria toxoid-containing vaccines contains aluminum as an adjuvant but no preservative. DTaP-HepB-IPV (Pediarix), DTaP-IPV/Hib (Pentacel), DTaP-IPV-Hib-HepB (Vaxelis), DTaP-IPV (Kinrix), and DTaP-IPV (Quadracel) contain neomycin and polymyxin B as antibiotics. DTaP-IPV-Hib-HepB (Vaxelis) contains streptomycin as an antibiotic. DTaP-HepB-IPV (Pediarix) and DTaP-IPV-Hib-HepB (Vaxelis) vaccines contain yeast protein. Presentations of some diphtheria toxoid-containing vaccines contain latex rubber.

Diphtheria Toxoid-containing Vaccine Characteristics

- Administered by intramuscular injection
- Contains aluminum as an adjuvant

Vaccination Schedule and Use

DTaP (Infanrix and Daptacel)

DTaP (diphtheria, tetanus toxoids, and acellular pertussis vaccine) is recommended for children age 6 weeks through 6 years. The routine schedule is a primary series of 3 doses at age 2, 4, and 6 months, a booster dose between age 15 through 18 months, and another booster dose between age 4 through 6 years (total of 5 doses). The first 3 doses should be given at 4- to 8-week intervals (minimum of 4 weeks). Dose 4 should follow dose 3 by no less than 6 months and should not be administered before age 12 months.

Dose 4 of both brands of DTaP is recommended to be administered at age 15 through 18 months (15 through 20 months for Daptacel). Dose 4 may be given as early as age 12 months if at least 6 months have elapsed since dose 3 and, in the

Diphtheria Toxoid-containing Vaccination Schedule

- DTaP
  - 3-dose primary series at age 2, 4, and 6 months
  - Primary series interval of 4- to 8-weeks and minimum interval 4 weeks
  - Boosters at age 15 through 18 months and age 4 through 6 years
  - Minimum interval for dose 4 is 6 months from dose 3 and minimum age is 12 months
  - If dose 4 is given on or after 4th birthday, the 5th dose is optional
  - DT is used in place of DTaP if child has a valid contraindication to pertussis vaccine

opinion of the vaccine provider, the child is unlikely to return for an additional visit between age 15 through 18 months.

Children who received 4 doses before their fourth birthday should receive a fifth dose of DTaP before entering school. The fifth dose is not necessary (but may be given) if dose 4 in the series was given on or after the fourth birthday. Administering the fifth dose increases antibody levels and may decrease the risk of school-age children transmitting the disease to younger siblings who are not fully vaccinated.

If a child has a valid contraindication to pertussis vaccine, DT should be used to complete the vaccination series. If the child was younger than age 12 months when the first dose of DT was administered (as DTP, DTaP, or DT), the child should receive a total of 4 DT doses. If the child was age 12 months or older at the time the first dose of DT was administered, 3 doses (with dose 3 administered 6 through 12 months after dose 2) will complete the primary DT series. If dose 4 of DTP, DTaP, or DT is administered before the fourth birthday, a fifth dose is recommended at age 4 through 6 years.

DTaP-HepB-IPV (Pediarix)

DTaP-HepB-IPV vaccine is approved for use as a 3-dose series for children age 6 weeks through 6 years. It is administered to infants at age 2, 4, and 6 months. The minimum intervals for DTaP-HepB-IPV vaccine are determined by the DTaP component. The 3 doses must be separated by at least 4 weeks between doses. Because the minimum age for the first dose of DTaP-HepB-IPV vaccine is 6 weeks, this vaccine cannot be used for the birth dose of hepatitis B (HepB) vaccine. The final dose of DTaP-HepB-IPV vaccine should be administered at age 24 weeks or older, the minimum age for completion of the hepatitis B vaccine series. When DTaP-HepB-IPV vaccine is used to provide 3 doses at age 2, 4, and 6 months (based on the DTaP and IPV schedules), this will result in a 4-dose HepB vaccine series, which is acceptable.

DTaP-IPV/Hib (Pentacel)

DTaP-IPV/Hib vaccine is approved for use as a 4-dose series for children age 6 weeks through 4 years. It is administered to infants at age 2, 4, 6, and 15 through 18 months. The minimum intervals for DTaP-IPV/Hib vaccine are determined by the DTaP component. The first 3 doses must be separated by at least 4 weeks between doses. Dose 4 must be separated from dose 3 by at least 6 months, and should not be administered before age 12 months. When DTaP-IPV/Hib vaccine is used to provide 4 doses at age 2, 4, 6, and between 15 through 18 months (based on the DTaP and Hib schedules), an additional booster dose with IPV-stand alone or DTaP-IPV vaccine should be administered at age 4 through 6 years. This will result in a 5-dose IPV vaccine series, which is acceptable.

DTaP-IPV-Hib-HepB (Vaxelis)

DTaP-IPV-Hib-HepB is approved for use as a 3-dose series for children age 6 weeks through 4 years. It is administered to infants at age 2, 4, and 6 months. The minimum intervals for DTaP-IPV-Hib-HepB vaccine are determined by the DTaP component. The 3 doses must be separated by at least 4 weeks between doses. Because the minimum age for the first dose of DTaP-IPV-Hib-HepB vaccine is 6 weeks, this vaccine cannot be used for the birth dose of hepatitis B (HepB) vaccine. The final dose of DTaP-IPV-Hib-HepB vaccine should be administered at age 24 weeks or older, the minimum age for completion of the hepatitis B vaccine series. When DTaP-IPV-Hib-HepB vaccine is used to provide 3 doses at age 2, 4, and 6 months (based on the DTaP and IPV schedules), this will result in a 4-dose HepB vaccine series, which is acceptable.

DTaP-IPV (Kinrix)

DTaP-IPV (Kinrix) vaccine is approved only for dose 5 of DTaP vaccine and dose 4 of IPV vaccine in children age 4 through 6 years whose previous DTaP vaccine doses have been with Infanrix and/or Pediarix for dose 1, 2, and 3 and Infanrix for dose 4. However, if DTaP-IPV (Kinrix) vaccine is administered to children who received another brand of DTaP vaccine for prior DTaP vaccine doses, or if administered as dose 1, 2, 3, or 4 of the DTaP vaccine series or dose 1, 2, or 3 of the IPV vaccine series, the dose of DTaP-IPV (Kinrix) does not need to be repeated.

DTaP-IPV (Quadracel)

DTaP-IPV (Quadracel) vaccine is approved only for dose 5 of DTaP vaccine and dose 4 or 5 of IPV vaccine in children age 4 through 6 years who have received 4 doses of Pentacel and/or Daptacel vaccine. However, if DTaP-IPV (Quadracel) vaccine is administered to children who received another brand of DTaP vaccine for prior DTaP vaccines doses, or if administered as dose 1, 2, 3, or 4 of the DTaP vaccine series or dose 1, 2, or 3 of the IPV series, the dose of DTaP-IPV (Quadracel) does not need to be repeated.

Tdap (Boostrix and Adacel) and Td (Tenivac and Tdvax)

Both Tdap vaccines are approved by the FDA for a booster dose for persons who have completed the recommended childhood DTP/DTaP vaccination series. Boostrix is approved for persons age 10 years or older. Adacel is approved for a single dose in persons age 10 through 64 years. A second dose of Adacel is also licensed for administration 8 or more years after the first Tdap dose and for use for tetanus prophylaxis when indicated for wound management if at least 5 years have elapsed since the previous receipt of any tetanus toxoid-containing vaccine. Both Td vaccines are approved for use in persons age 7 years or older.

Diphtheria Toxoid-containing Vaccination Schedule

- Tdap
  - 1 dose at age 11 through 18 for adolescents who have completed DTaP series
  - Booster dose of Td or Tdap every 10 years for all persons

Diphtheria

Use of Tdap

- 1 dose Tdap during each pregnancy (off-label use)
- 1 dose Tdap for the following with no previous documentation of Tdap: adults, adolescents and adults who have or anticipate having close contact with an infant younger than age 12 months, and health care personnel
- 3 doses of tetanus- and diphtheria-containing vaccine (1 dose should be Tdap) for adolescents and adults without documentation of a primary series

A single Tdap dose is recommended for adolescents age 11 through 18 years who have completed the recommended childhood DTP/DTaP vaccination series, preferably at age 11 through 12 years. Adults age 19 years or older who have not previously received Tdap should receive a single dose of Tdap. To reduce the burden of pertussis in infants, a dose of Tdap has been recommended during each pregnancy since 2012, although this practice is an off-label use.

All adolescents and adults should have received a primary series of at least 3 documented doses of tetanus and diphtheria toxoids-containing vaccine (i.e., DTaP, DTP, DT, or Td) during their lifetime. A person without such documentation should receive a series of 3 doses of tetanus- and diphtheria-containing vaccine. One of these doses, preferably the first, should be Tdap. The remaining 2 doses should be either Td or Tdap.

For persons age 7 to 9 years who receive a dose of Tdap as part of the catch-up series, an adolescent Tdap dose should be administered at age 11 through 12 years. If a Tdap dose is administered at age 10 years or older, the Tdap dose may count as the adolescent Tdap dose. Either brand of Tdap may be used.

Adults age 19 years or older who previously have not received Tdap should receive a single dose of Tdap to protect against pertussis and reduce the likelihood of transmission. For adults age 19 through 64 years, either brand of Tdap may be used. Adults age 65 years or older should be vaccinated with Boostrix, if feasible. However, either vaccine administered to a person age 65 years or older is immunogenic and would provide protection. A dose of either vaccine would be considered valid.

Adolescents and adults who have not previously received Tdap, and have or anticipate having close contact with an infant younger than age 12 months (e.g., parents, siblings, grandparents, child care providers, and health care personnel) should receive a single dose of Tdap to protect against pertussis. Ideally, these persons should receive Tdap at least 2 weeks before beginning close contact with the infant.

Health care personnel should receive a single dose of Tdap as soon as feasible if they have not previously received Tdap, regardless of the time since their most recent Td vaccination.

When Tdap is indicated (e.g., routine vaccination, catch-up vaccination, or pregnancy), it can be administered regardless of the interval since the last tetanus- or diphtheria-toxoid-containing vaccine. After receipt of Tdap, persons should continue to receive a dose of Td or Tdap for routine booster immunization against tetanus and diphtheria every 10 years unless needed sooner for tetanus prophylaxis as part of wound management.

Immunogenicity and Vaccine Efficacy

After a primary series of 3 properly spaced doses of diphtheria toxoid-containing vaccines in infants and a booster dose at age 15 through 18 months or 3 properly spaced doses in adults, a protective level of antitoxin (defined as greater than 0.1 IU of antitoxin/mL) is reached in more than 95% of vaccine recipients. Diphtheria toxoid-containing vaccine has been estimated to have an efficacy of 97%.

Diphtheria Toxoid-containing Vaccine Efficacy

- More than 95% of recipients develop protective antibody levels after 3 doses and booster (infants) or 3 doses (adults).

Contraindications and Precautions to Vaccination

As with other vaccines, a history of a severe allergic reaction (anaphylaxis) to a vaccine component or following a prior dose is a contraindication to further doses. Moderate or severe acute illness (with or without fever) in a patient is considered a precaution to vaccination, although persons with minor illness may be vaccinated.

Contraindications to combination vaccines that contain DTaP include the contraindications to the individual component vaccines (e.g., IPV, hepatitis B, Hib), but specific ingredients might differ. DTaP-HepB-IPV (Pediarix) and DTaP-IPV-Hib-HepB (Vaxelis) vaccines contain yeast. Presentations of some diphtheria toxoid-containing vaccines contain latex rubber. DTaP-HepB-IPV (Pediarix), DTaP-IPV/Hib (Pentacel), DTaP-IPV-Hib-HepB (Vaxelis), DTaP-IPV (Kinrix), and DTaP-IPV (Quadracel) contain neomycin and polymyxin B. DTaP-IPV-Hib-HepB (Vaxelis) contains streptomycin.

Encephalopathy not attributable to another identifiable cause occurring within 7 days after vaccination with DTaP, DTP, or Tdap is a contraindication for DTaP and Tdap vaccination.

A progressive or unstable neurological disorder, uncontrolled seizures, or progressive encephalopathy is a precaution for DTaP and Tdap vaccination. For persons with a known or suspected neurologic condition, vaccination with DTaP or Tdap should be delayed until the condition has been evaluated, treatment initiated, and the condition stabilized. These conditions include the presence of an evolving neurologic disorder (e.g., uncontrolled epilepsy, infantile spasms, and progressive encephalopathy); a history of seizures that has not been evaluated; or a neurologic event that occurs between doses of 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 neither contraindications nor precautions to DTaP or Tdap vaccination.

Diphtheria and Tetanus Toxoids-containing Vaccine Contraindications and Precautions

- Contraindication
  - Severe allergic reaction to vaccine component or following a prior dose
  - Encephalopathy not attributable to another identifiable cause within 7 days after vaccination*
- Precaution
  - Moderate or severe acute illness
  - Progressive or unstable neurological disorder*
  - Uncontrolled seizures*
  - Progressive encephalopathy*
  - Guillain-Barré syndrome within 6 weeks after a previous dose of tetanus toxoid-containing vaccine**
  - History of Arthus-type hypersensitivity reactions after a previous dose of diphtheria toxoid- or tetanus toxoid-containing vaccine**

*DTaP and Tdap

**DTaP, DT, Tdap, Td

Diphtheria Toxoid-containing Vaccine Safety

DTaP

- Pain, redness, or swelling
  - 20%-40%
  - More frequent after dose 4 or 5
- Temperature of 101°F
  - 3%-5%
- Moderate or severe systemic reactions
  - Fewer than 1 in 10,000 doses
- Arthus-type reactions are rare

Tdap, Td

- Pain, redness, or swelling
  - 21%-75%
- Temperature of 100.4°F or higher
  - 1.1%-5%

Guillain-Barré syndrome within 6 weeks after a previous dose of tetanus toxoid-containing vaccine is a precaution for DTaP, Tdap, DT, and Td vaccination.

A history of Arthus-type hypersensitivity reactions after a previous dose of diphtheria toxoid-containing or tetanus toxoid-containing vaccine is a precaution for DTaP, Tdap, DT, and Td vaccination; vaccination should be deferred until at least 10 years have elapsed since the last tetanus toxoid-containing vaccine.

Vaccine Safety

DTaP vaccine may cause local reactions, such as pain, redness, or swelling. Local reactions have been reported in 20% to 40% of children after each of the first 3 doses. Local reactions appear to be more frequent after the fourth and/or fifth doses. Mild systemic reactions such as drowsiness, fretfulness, and low-grade fever may also occur. Temperature of 101°F or higher is reported in 3% to 5% of DTaP recipients. These reactions are self-limited and can be managed with symptomatic treatment with acetaminophen or ibuprofen.

Moderate or severe systemic reactions (such as fever of 105°F or higher, febrile seizures, persistent crying lasting 3 hours or longer, and hypotonic-hyporesponsive episodes) have been reported after administration of DTaP, but occur less frequently than among children who received whole-cell DTP. Rates of moderate or severe systemic reactions vary by symptom and vaccine but generally occur in fewer than 1 in 10,000 doses.

Exaggerated local (Arthus-type) reactions are rarely reported but may occur following receipt of a vaccine containing diphtheria or tetanus toxoids.

The most common adverse reaction following vaccination with both brands of Tdap is a local reaction, such as pain (66% to 75%), redness (25%), or swelling (21%) at the site of injection. Temperature of 100.4°F or higher was reported by 1.4% to 5% of Tdap recipients and 1.1% to 5% of Td recipients. Tdap recipients also reported a variety of nonspecific systemic events, such as headache, fatigue and gastrointestinal symptoms.

The Institute of Medicine reported in 2011 that the evidence was inadequate to accept or reject a causal relation between receipt of diphtheria toxoid and tetanus toxoid-containing vaccine and encephalitis, encephalopathy, infantile spasms, seizures, ataxia, autism, acute disseminated encephalomyelitis, transverse myelitis, optic neuritis, onset of multiple sclerosis in adults, relapse of multiple sclerosis in adults, relapse of multiple sclerosis in children, Guillain-Barré syndrome, chronic inflammatory disseminated polyneuropathy, opsoclonus myoclonus syndrome, or Bell's palsy.

The most frequently reported adverse events after DTaP in the Vaccine Adverse Effect Reporting System (VAERS) and Vaccine Safety Datalink (VSD), two post-licensure surveillance systems, were consistent with observations from pre-licensure studies of these vaccines. When VAERS DTaP reports for each vaccine brand were compared individually with reports for all other inactivated vaccines in the VAERS database, no concerning patterns of adverse events were observed.

Routine VAERS surveillance for and VSD studies on adverse events following receipt of Tdap vaccines in persons aged 10 through 64 years have provided reassuring data consistent with the prelicensure clinical trial safety data and have not demonstrated any associations between Tdap and the following rare adverse events: encephalopathy-encephalitis-meningitis, paralytic syndromes, seizures, cranial nerve disorders, and Guillain-Barré syndrome.

Vaccine Storage and Handling

DTaP, Td, and Tdap vaccines should be maintained at refrigerator temperature between 2°C and 8°C (36°F and 46°F). Manufacturer package inserts contain additional information. For complete information on best practices and recommendations, please refer to CDC's Vaccine Storage and Handling Toolkit, www.cdc.gov/vaccines/hcp/admin/storage/toolkit/storage-handling-toolkit.pdf.

Surveillance and Reporting of Diphtheria Disease

In January 2019, the Council of State and Territorial Epidemiologists modified its diphtheria case definition. This modification specifies that toxigenic diphtheria infections from any anatomic site (such as skin), not only respiratory infections, should be reported. In addition, confirmed case classification requires verification of toxin production by the *C. diphtheriae* isolate. For information on guidance for state and local health department staff who are involved in surveillance activities for vaccine-preventable diseases, please consult the Manual for the Surveillance of Vaccine-Preventable Diseases, www.cdc.gov/vaccines/pubs/surv-manual/chapters.html.

Acknowledgements

The editors would like to acknowledge Susan Hariri, Fiona Havers, and Jennifer Liang for their contributions to this chapter.

NOTES

Selected References

American Academy of Pediatrics. Diphtheria. In: Kimberlin D, Brady M, Jackson M, et al., eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics 2018:319–23.

CDC. Diphtheria, tetanus, and pertussis: Recommendations for vaccine use and other preventive measures: recommendations of the Immunization Practices Advisory Committee (ACIP). *MMWR* 1991;40(No. RR-10):1–28.

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(No. RR-7):1–25.

CDC. Preventing tetanus, diphtheria, and pertussis among adolescents: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccines. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2006;55(No. RR-3):1–34.

CDC. Preventing tetanus, diphtheria, and pertussis among adults: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccines. Recommendations of the Advisory Committee on Immunization Practices (ACIP) and recommendation of ACIP, supported by the Healthcare Infection Control Practices Advisory Committee (HICPAC) for Use of Tdap Among Health-Care Personnel. *MMWR* 2006;55(No. RR-17):1–33.

CDC. Prevention of Pertussis, Tetanus, and Diphtheria with Vaccines in the United States: Recommendation of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2018;67(RR-2):1–44.

CDC. Use of Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Vaccines: Updated Recommendations of the Advisory Committee on Immunization Practices – United States, 2019. *MMWR* 2020;69(3):77–83.

Griffith J, Bozio C, Poel A, et al. Imported Toxin-Producing Cutaneous Diphtheria — Minnesota, Washington, and New Mexico, 2015–2018. *MMWR* 2019;68(12):281–4.

Otshudiema J, Acosta A, Cassiday P, et al. Respiratory illness caused by Corynebacterium diphtheriae and C. ulcerans, and use of diphtheria anti-toxin in the United States, 1996-2018, *Clin Infect Dis* 2020;ciaa1218. Doi: https://doi.org/10.1093/cid/ciaa1218.

Tiwari T, Wharton M. Diphtheria toxoid. In: Plotkin S, Orenstein W, Offit, P, et al., eds. Plotkin's *Vaccines*. 7th ed. Elsevier;2018:261–75.

Vitek C, Wharton M. Diphtheria in the former Soviet Union: reemergence of a pandemic disease. *Emerg Infect Dis* 1998;4:539–50.

Haemophilus influenzae type B

Sara E. Oliver, MD, MSPH; Pedro Moro, MD, MPH; and Amy E. Blain, MPH

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

In the 1930s, Margaret Pittman demonstrated that *H. influenzae* could be isolated in encapsulated (typeable) and unencapsulated (nontypeable) forms. She 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, primarily among children younger than age 5 years; approximately one in 200 children in this age group developed invasive Hib disease. Approximately two-thirds of all cases occurred among children younger than age 18 months.

A pure polysaccharide vaccine was licensed for use in the United States in 1985 and was used until 1988. The first Hib conjugate vaccine was licensed in 1987.

***Haemophilus influenzae* type b**

- Causes severe bacterial infection, particularly among infants
- During late 19th century believed to cause influenza
- Immunology and microbiology clarified in 1930s
- Leading cause of bacterial meningitis during prevaccine era

Haemophilus influenzae

H. influenzae, a fastidious, pleomorphic, gram-negative coccobacillus, requires hemin (X factor) and nicotinamide-adenine-dinucleotide (NAD, also known as V factor) for in vitro growth. It is generally aerobic, but can grow as an anaerobe under certain conditions.

The outermost structure of encapsulated *H. influenzae* is composed of a polysaccharide, a key virulence factor. Six antigenically and biochemically distinct capsular polysaccharide types have been described; these are designated serotypes a through f. Hib capsule is composed of polyribosyl-ribitol-phosphate (PRP), a polysaccharide used in Hib vaccines. There are currently no vaccines to prevent disease caused by non-b encapsulated or nontypeable strains. In the pre-Hib-vaccine era, type b organisms accounted for 95% of all *H. influenzae* strains that caused invasive disease.

Hib does not survive in the environment on inanimate surfaces.

Haemophilus influenzae

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

Hib Pathogenesis

- Enters and colonizes nasopharynx
- May cause an invasive infection—invades bloodstream and infects distant sites in the body
- Incidence is age-dependent; peak occurrence was age 6 to 11 months*
- Most children acquired immunity by age 5 or 6 years*

*Prevaccine era

Pathogenesis

H. influenzae 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% to 3% of healthy infants and children, but was uncommon in adults. Nontypeable strains also frequently inhabit the human respiratory tract.

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

Incidence is strikingly age-dependent. In the prevaccine era, up to 60% of invasive disease occurred before age 12 months, although some infants received passive protection from maternal IgG antibodies passed through the placenta and breastfeeding during the first 6 months of life. Peak occurrence was among children age 6 to 11 months.

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

In the prevaccine era, most children acquired immunity by age 5 or 6 years through asymptomatic nasopharyngeal carriage of Hib bacteria. Since only a relatively small proportion of children carry Hib at any time, it has been assumed 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 higher the age-specific incidence of Hib disease, the less likely there will be acquisition of both anticapsular and serum bactericidal antibody.

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

Clinical Features

Hib can affect many organ systems. The most common types of disease are meningitis, bacteremia, epiglottitis, pneumonia, arthritis, and cellulitis.

Meningitis, an infection of the membranes covering the brain and spinal cord, is the most common clinical manifestation of invasive Hib disease, accounting for 50% to 65% of cases in the prevaccine era. Hallmarks of meningitis are fever, decreased mental status, and stiff neck. Hearing impairment or other neurologic sequelae occur in 15% to 30% of survivors. The case fatality ratio is 3% to 6%, despite appropriate antimicrobial therapy.

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

Septic arthritis, cellulitis, and pneumonia (which can be mild focal or severe empyema) are common manifestations of invasive Hib disease. Osteomyelitis and pericarditis are less common forms of invasive disease.

Otitis media and acute bronchitis due to *H. influenzae* are generally caused by nontypeable strains. Hib strains account for only 5% to 10% of *H. influenzae* causing otitis media.

Non-type b encapsulated strains can cause invasive disease similar to type b infections. Nontypeable strains are generally less virulent than encapsulated strains among previously healthy individuals, but may cause invasive disease, particularly among neonates and those older than age 65 years.

Hib Clinical Features

- Most common diseases resulting from Hib infection are meningitis, bacteremia, epiglottitis, pneumonia, arthritis, and cellulitis
- Generally requires hospitalization and 10 days of antimicrobial therapy
- Meningitis accounted for 50% to 65% of cases with a fatality ratio of 3% to 6% (prevaccine era)

Laboratory Testing

A Gram stain of an infected body fluid may demonstrate small, gram-negative coccobacilli suggestive of *H. influenzae* disease. CSF, blood, pleural fluid, joint fluid, and middle ear aspirates should be cultured on appropriate media. A positive culture for *H. influenzae* establishes the diagnosis. Detection of antigen or DNA may be used as an adjunct to culture, particularly in diagnosing *H. influenzae* infection in patients who have been partially treated with antimicrobial agents, in which case the organism may not be viable on culture.

All isolates of *H. influenzae* should be serotyped. This is an extremely important laboratory procedure that should be performed on every isolate of *H. influenzae*, especially those obtained from children younger than age 15 years. Two tests are available for serotyping isolates: slide agglutination and serotype-specific, real-time polymerase chain reaction (PCR). Slide agglutination is used 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 because of false positives. Serotype-specific, real-time PCR, currently available to detect the specific target gene of each serotype, can be used for detection of *H. influenzae* in blood, CSF, or other clinical specimens.

Serotype-specific tests, usually done by a state health department or reference laboratory, indicate whether an isolate is type b, the only serotype that is potentially vaccine-preventable.

Medical Management

Invasive Hib disease generally requires hospitalization. Antimicrobial therapy with an effective, third-generation cephalosporin (cefotaxime or ceftriaxone) should be started immediately. Chloramphenicol in combination with ampicillin could be used as an alternative. The treatment course is usually 10 days. Ampicillin-resistant strains of Hib are now common throughout the United States. Children with life-threatening illness in which Hib may be the etiologic agent should not receive ampicillin alone as initial therapy.

Hib Epidemiology

- Reservoir
  - Human
- Transmission
  - Person-to-person through droplet inhalation or direct contact with respiratory tract
  - Neonates can acquire during delivery through amniotic fluid or contact with genital tract secretions
- Temporal pattern
  - Bimodal: peaks in Sept–Dec and March–May
- Communicability
  - Generally limited but higher in some circumstances

Epidemiology

Occurrence

Hib disease occurs worldwide.

Reservoir

Humans are the only known reservoir.

Transmission

H. influenzae colonizes the upper respiratory tract of humans and is transmitted person-to-person by inhalation of respiratory droplets or by direct contact with respiratory tract secretions. Neonates can acquire infection by aspiration of amniotic fluid or contact with genital tract secretions during delivery.

Temporal Pattern

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

Communicability

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

Risk Factors

Risk factors for Hib disease include both exposure factors and host factors. Exposure factors include household crowding, large household size, child care attendance, low socioeconomic status, low parental education levels, and school-age siblings. Host factors include age (youngest and oldest ages with elevated risk), race/ethnicity (Native Americans with an elevated risk, possibly confounded by socioeconomic variables associated with both race/ethnicity and Hib disease), and chronic disease (e.g., functional and anatomic asplenia, human immunodeficiency virus [HIV] infection, immunoglobulin deficiency, complement deficiency, receipt of chemotherapy or stem cell transplant). Protective factors (for infants younger than age 6 months) include breastfeeding and passively acquired maternal antibody.

Data are conflicting on the risk for secondary illness among child care contacts, but the risk is thought to be lower than among household contacts. Most studies suggest child care contacts are at relatively low risk for secondary transmission of Hib disease, particularly if contacts are appropriately vaccinated.

Secular Trends in the United States

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

Active Bacterial Core surveillance (ABCs) data includes serotype information on all invasive *H. influenzae* isolates. The number of cases and deaths of invasive *H. influenzae* infections in the United States increased from 3,400 in 1997 to 6,840 in 2018. Approximately 11.8% of cases died. While the rate of invasive *H. influenzae* infections increased from 1.23 per 100,000 population in 1997 to 2.08 per 100,000 population in 2018 in the surveillance areas, the rate of Hib infections decreased from 0.1 per 100,000 population in 1997 to 0.02 per 100,000 population in 2018. Among children younger than age 5 years in 2018, the rate of invasive *H. influenzae* disease was 0.08 per 100,000 population and 38 cases of invasive disease due to Hib were reported in the United States. An additional 9 cases of Hib are estimated to have occurred among the 175 reports of invasive *H. influenzae* infections with an unknown serotype.

Hib Secular Trends in the United States

- About 20,000 cases of Hib annually before vaccine
- Incidence of Hib has declined 99% since the prevaccine era
- From 2009-2018, 36 reported cases of Hib in patients younger than age 5 years
- Secondary cases of Hib are rare (illness occurring 1-60 days following contact with an ill person)

From 2009–2018, 36 Hib cases in patients younger than age 5 years were reported to ABCs. Two (5.6%) were too young to have received Hib vaccine, 12 (33.3%) were unvaccinated, and 14 (38.9%) were undervaccinated (10 of 14 had received the 3-dose primary series but were missing a booster dose at age 12 through 15 months). Eight (22.2%) were age-appropriately vaccinated and had no reported underlying conditions; three of these were 3-month-old infants who had been age-eligible for only the first dose of Hib vaccine.

Secondary cases of Hib disease occur but are rare. Secondary Hib disease is defined as illness occurring 1 to 60 days following contact with an ill person, and accounts for less than 5% of all invasive Hib disease. Secondary attack rates are higher among household contacts younger than age 48 months (2.1%), especially those younger than age 12 months (6%) and younger than age 24 months (3%). In these household contacts, 64% of secondary cases occurred within the first week (excluding the first 24 hours) of disease onset in the index patient, 20% during the second week, and 16% during the third and fourth weeks.

Among children born during 2016–2017, 92.2% had received the Hib vaccine primary series (at least 2 or 3 doses, depending on product) and 79.9% had received the full series (primary series and booster; at least 3 or 4 doses, depending on product type) by age 24 months.

Hib Vaccines

- Three conjugate vaccines
  - PRP-T (ActHIB)
  - PRP-T (Hiberix)
  - PRP-OMP (PedvaxHIB)
- Two combination vaccines containing Hib
  - DTaP-IPV/Hib (Pentacel)
  - DTaP-IPV-Hib-HepB (Vaxelis)

Haemophilus influenzae type b Vaccines

A pure polysaccharide vaccine was licensed for use in the United States in 1985 and was used until 1988. The vaccine had low efficacy and is no longer available in the United States.

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

The first Hib conjugate vaccine was licensed in 1987. Conjugation is the process of chemically bonding a polysaccharide to a more effective protein carrier. 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 conjugate vaccines elicit booster responses and allow maturation of class-specific immunity with predominance of IgG antibody. The conjugates also cause carrier priming and elicit antibody to "useful" carrier protein.

Three monovalent Hib polysaccharide-protein conjugate vaccines (ActHIB, PedvaxHIB, and Hiberix) are currently licensed for use in the United States.

Two combination vaccines containing Hib are currently licensed for use, DTaP-IPV/Hib (Pentacel) and DTaP-IPV-Hib-HepB (Vaxelis).

Characteristics

Hib (PRP-T [ActHIB, Hiberix]) use a tetanus toxoid carrier protein, while Hib (PRP-OMP [PedvaxHIB]) uses a meningococcal outer membrane protein. DTaP-IPV/Hib (Pentacel) contains Hib (PRP-T) and DTaP-IPV-Hib-HepB (Vaxelis) contains Hib (PRP-OMP). Hib vaccines are administered by intramuscular injection. Each dose of Hib (PRP-OMP [PedvaxHIB]) vaccine contains aluminum as an adjuvant. Monovalent Hib vaccines contain no antibiotic or preservative. Specific ingredients to combination vaccines containing Hib vaccine differ.

Hib Vaccine Characteristics

- PRP-T use a tetanus toxoid carrier protein
- PRP-OMP uses a meningococcal outer membrane protein
- Administered by intramuscular injection
- PRP-OMP doses contain aluminum adjuvant

Vaccination Schedule and Use

All infants should receive a primary series of Hib conjugate vaccine (monovalent or combination vaccine) beginning at age 2 months. The number of doses in the primary series depends on the type of vaccine used. A primary series of Hib (PRP-T) requires 3 doses, whereas Hib (PRP-OMP) requires 2 doses. A booster dose is recommended at age 12 through 15 months, regardless of which vaccine is used for the primary series. The recommended age for dose 4 of DTaP-IPV/Hib is age 15 through 18 months, but it can be administered as early as age 12 months, provided at least 6 months have elapsed since dose 3.

Haemophilus influenzae type B

Hib Vaccination Schedule (Monovalent Vaccines)

- PRP-T (ActHIB and Hiberix) 3-dose primary series at age 2, 4, and 6 months
- PRP-OMP (PedvaxHIB) 2-dose primary series at age 2 and 4 months
- Booster dose at age 12 through 15 months
- Recommended interval between primary series doses is 8 weeks and minimum interval is 4 weeks
- Minimum age for dose 1 is 6 weeks
- Catch-up recommendations depend on child's age
- Vaccines are interchangeable and should follow a 3-dose schedule if more than 1 brand is used

Haemophilus influenzae type b (Hib) Routine Vaccination Schedule

Vaccine type	Vaccine Trade Names	2 months	4 months	6 months	12–15 months
PRP-T	ActHIB	Dose 1	Dose 2	Dose 3	Booster
	Pentacel	Dose 1	Dose 2	Dose 3	Booster*
	Hiberix	Dose 1	Dose 2	Dose 3	Booster†
PRP-OMP	PedvaxHIB	Dose 1	Dose 2	—	Booster
	Vaxelis	Dose 1	Dose 2	Dose 3§	Not indicated

* The recommended age for dose 4 of DTaP-IPV/Hib (Pentacel) is age 15 through 18 months, but it can be administered as early as 12 months, provided at least 6 months have elapsed since dose 3.

† The recommended age for dose 4 of Hib (PRP-T) (Hiberix) is age 15 months, but to facilitate timely booster vaccination, it may be administered as early as age 12 months.

§The recommended minimum age for dose 3 of DTaP-IPV-Hib-HepB (Vaxelis) is 24 weeks, the minimum age for completion of the hepatitis B vaccine series.

The recommended interval between doses in the primary series is 8 weeks, with a minimum interval of 4 weeks. At least 8 weeks should separate the booster dose from the previous (2nd or 3rd) dose. If DTaP-IPV/Hib is administered for the booster dose, at least 6 months need to have elapsed since dose 3.

Hib vaccines should be given at the same visit as other recommended vaccines.

Limited data suggest Hib conjugate vaccines administered before age 6 weeks can induce immunologic tolerance, reducing the response to subsequent doses of Hib vaccine. Therefore, Hib vaccines, including combination vaccines containing Hib conjugate vaccine, should never be administered to a child younger than age 6 weeks.

The monovalent Hib conjugate vaccines are interchangeable. A series that includes vaccine of more than one brand will induce a protective antibody level. If a child receives different brands of Hib vaccine at age 2 and 4 months, a 3rd dose of any brand should be administered at age 6 months to complete the primary series. Any of these vaccines may be used for the booster dose, regardless of which vaccines were administered for the primary series. Data on the interchangeability of Hib combination vaccine with monovalent vaccines are limited. Whenever feasible, the same combination vaccine should be used for the subsequent doses.

Unvaccinated children age 7 months or 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.

Haemophilus influenzae type b Vaccine Schedule for Previously Unvaccinated Children

Vaccine	Age at 1st Dose (months)	Primary series	Booster
PRP-T	2–6	3 doses, each dose 8 weeks apart	12–15 months
	7–11	2 doses, 4 weeks apart	12–15 months
	12–14	1 dose	8 weeks later
	15–59	1 dose	--
PRP-OMP	2–6	2 doses, 8 weeks apart	12–15 months
	7–11	2 doses, 4 weeks apart	12–15 months
	12–14	1 dose	8 weeks later
	15–59	1 dose	—

PRP-T (ActHIB, Hiberix)

Unvaccinated infants age 2 through 6 months should receive 3 doses of vaccine, administered 2 months apart. The primary series should be followed by a booster dose at age 12 through 15 months, administered at least 8 weeks after the last dose. A booster dose is only needed if 2 or 3 primary doses were administered before age 12 months. Unvaccinated children age 7 through 11 months should receive 2 doses of vaccine, 4 weeks apart. Those 2 doses should be followed by a booster dose at age 12 through 15 months, administered at least 8 weeks after the last dose. Unvaccinated children age 12 through 14 months should receive 1 dose of vaccine, followed by a booster dose at least 8 weeks later. Any previously unvaccinated child age 15 through 59 months should receive a single dose of vaccine.

PRP-OMP (PedvaxHIB)

Unvaccinated infants age 2 through 6 months should receive 2 doses of vaccine, administered 2 months apart. Those 2 doses should be followed by a booster dose at age 12 through 15 months, administered at least 8 weeks after the last dose. Unvaccinated children age 7 through 11 months should receive 2 doses of vaccine, 4 weeks apart, followed by a booster dose at age 12 through 15 months. The booster should be administered

at least 8 weeks after the last dose. Unvaccinated children age 12 through 14 months should receive 1 dose of vaccine, followed by a booster at least 8 weeks later. Any previously unvaccinated child age 15 through 59 months should receive a single dose of vaccine.

DTaP-IPV/Hib (Pentacel)

DTaP-IPV/Hib vaccine is approved for use as a 4-dose series for children age 6 weeks through 4 years. It is administered to infants at age 2, 4, 6, and 15 through 18 months. The minimum intervals for DTaP-IPV/Hib vaccine are determined by the DTaP component. The first 3 doses must be separated by at least 4 weeks between doses. Dose 4 must be separated from dose 3 by at least 6 months, and should not be administered before age 12 months. When DTaP-IPV/Hib vaccine is used to provide 4 doses at age 2, 4, 6, and between 15 through 18 months (based on the DTaP and Hib schedules), an additional booster dose with IPV-stand alone or DTaP-IPV vaccine should be administered at age 4 through 6 years. This will result in a 5-dose IPV vaccine series, which is acceptable.

DTaP-IPV-Hib-HepB (Vaxelis)

DTaP-IPV-Hib-HepB is approved for use as a 3-dose series for children age 6 weeks through 4 years. It is administered to infants at age 2, 4, and 6 months. The minimum intervals for DTaP-IPV-Hib-HepB vaccine are determined by the DTaP component. The 3 doses must be separated by at least 4 weeks between doses. Because the minimum age for the first dose of DTaP-IPV-Hib-HepB vaccine is 6 weeks, this vaccine cannot be used for the birth dose of hepatitis B (HepB) vaccine. The final dose of DTaP-IPV-Hib-HepB vaccine should be administered at age 24 weeks or older, the minimum age for completion of the hepatitis B vaccine series. When DTaP-IPV-Hib-HepB vaccine is used to provide 3 doses at age 2, 4, and 6 months (based on the DTaP and IPV schedules), this will result in a 4-dose HepB vaccine series, which is acceptable.

While single antigen PRP-OMP Hib vaccines are licensed as a 2-dose primary series at age 2 and 4 months, DTaP-IPV-Hib-HepB is licensed as a 3-dose primary series. Therefore, three doses of a Hib conjugate-containing vaccine are needed to complete the primary series if DTaP-IPV-Hib-HepB is used for any doses. DTaP-IPV-Hib-HepB should not be used for the booster dose (given after completion of the 3-dose primary series). Any Hib conjugate vaccine licensed for a booster dose can be used. If DTaP-IPV-Hib-HepB is inadvertently given for the booster dose, the dose does not need to be repeated with another Hib-containing vaccine, if the proper spacing of prior doses is maintained.

Vaccination of Special Populations and Older Children

Children younger than age 24 months who develop invasive Hib disease should be considered susceptible and should receive Hib vaccine. Vaccination of these children should start as soon as possible during the convalescent phase of the illness. A complete series as recommended for the child's age should be administered.

Children age 12 through 59 months who are at increased risk for Hib disease, including chemotherapy recipients and those with anatomic and functional asplenia (including sickle-cell disease), HIV infection, immunoglobulin deficiency, or early complement component deficiency, who have received either no doses or only 1 dose of Hib vaccine before age 12 months, should receive 2 additional doses of Hib vaccine, 8 weeks apart. Children who received 2 or more doses of Hib vaccine before age 12 months should receive 1 additional dose.

If a child younger than age 5 years undergoing chemotherapy or radiation treatment received a Hib vaccine dose(s) within 14 days of starting therapy or during therapy, they should receive a repeat dose(s) at least 3 months following therapy completion.

In general, Hib vaccination of persons older than age 59 months is not recommended. The majority of older children are immune to Hib, probably from asymptomatic infection as infants. However, some older children and adults are at increased risk for invasive Hib disease and may be vaccinated if they were not vaccinated in childhood. A single dose of any Hib-containing vaccine should be administered to persons age 15 months or older undergoing an elective splenectomy if they are considered unimmunized. "Unimmunized" means they have not received a primary series and booster dose or at least 1 dose of Hib vaccine after age 14 months. If possible, the vaccine should be administered at least 14 days before the procedure. Hib vaccine should be administered to children age 5 years or older and adults who have anatomic or functional asplenia if they are considered unimmunized. Hib vaccine should be administered to children and adolescents age 5 through 18 years if they have HIV and are considered unimmunized. Adults with HIV do not need a dose of Hib vaccine. Hematopoietic stem cell transplant recipients of any age should receive 3 doses of Hib vaccine at least 4 weeks apart, beginning 6 to 12 months post-transplant, regardless of Hib vaccination history.

For American Indians/Alaska Natives (AI/AN), the Advisory Committee on Immunization Practices (ACIP) recommends Hib (PRP-OMP) as the preferred vaccine for the primary series doses. Hib meningitis incidence peaks at a younger age among AI/AN infants, and Hib (PRP-OMP) produces a protective antibody response after the first dose, providing early protection.

Hib Vaccination of Special Populations and Older Children

- Children younger than age 24 months who develop invasive Hib
  - Vaccinate as soon as possible during convalescent phase
  - Administer complete series for age
- Children age 12 through 59 months at increased risk (chemotherapy, anatomic and functional asplenia, HIV infection, immunoglobulin deficiency, early complement component deficiency)
  - If child received 0 or 1 dose before age 12 months, administer 2 doses, 8 weeks apart
  - If child received 2 or more doses before age 12 months, administer 1 dose
- Unimmunized persons age 15 months or older undergoing an elective splenectomy
  - Administer 1 dose at least 14 days before procedure
- Unimmunized persons age 5 years or older with anatomic or functional asplenia
  - Administer 1 dose
- Unimmunized children and adolescents age 5 through 18 years with HIV
  - Administer 1 dose
- Hematopoietic stem cell transplant recipients of any age
  - Administer 3 doses at least 4 weeks apart, beginning 6 to 12 months post-transplant
- American Indians/Alaska Natives
  - Administer PRP-OMP as preferred vaccine

Hib Vaccine Efficacy

- Highly immunogenic
- More than 95% of infants develop protective antibody levels after a primary series

Immunogenicity and Vaccine Efficacy

Hib conjugate vaccines are highly immunogenic. More than 95% of infants develop protective antibody levels after a primary series. Clinical efficacy has been estimated at 95% to 100%. Invasive Hib disease is uncommon in children who are fully vaccinated.

Hib vaccine is also immunogenic in patients at increased risk for invasive disease, such as those with sickle-cell disease, leukemia, or those who have had a splenectomy. 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.

Hib Vaccine Contraindications and Precautions

- Contraindication
  - Severe allergic reaction to a vaccine component or following a prior dose of vaccine
  - Children younger than age 6 weeks
- Precaution
  - Moderate or severe acute illness

Contraindications and Precautions to Vaccination

As with other vaccines, a history of a severe allergic reaction (anaphylaxis) to a vaccine component or following a prior dose is a contraindication to further doses. Moderate or severe acute illness with or without fever in a patient is considered a precaution to vaccination, although persons with minor illness may be vaccinated.

Hib conjugate vaccines are contraindicated for children younger than age 6 weeks because of the potential for development of immunologic tolerance.

Contraindications to combination vaccines that contain Hib include the contraindications to the individual component vaccines, but specific ingredients might differ.

Hib Vaccine Safety

- Adverse reactions uncommon
- Swelling, redness, or pain
  - 5%–30%
- Fever
  - 31%
- Crying
  - 11%
- Injection site erythema
  - 11%
- Irritability
  - 10%
- Rash
  - 9%

Vaccine Safety

Adverse reactions following Hib conjugate vaccines are not common. Swelling, redness, or pain have been reported in 5% to 30% of recipients and usually resolve within 12 to 24 hours. Systemic reactions such as fever and irritability are infrequent.

Among reports to the Vaccine Adverse Event Reporting System (VAERS) following Hib vaccination, the most frequently reported adverse events were fever (31%), crying (11%), injection site erythema (11%), irritability (10%), and rash (9%). The median time from vaccination to onset of an adverse event was 1 day. The adverse event reporting frequencies for Hib vaccines are similar to those of other childhood vaccines; no unusual or unexpected safety concerns were observed in VAERS data for Hib vaccines.

In an observational study conducted by the Vaccine Safety Datalink of DTaP-IPV/Hib, children age 1 to 2 years who received DTaP-IPV/Hib had an elevated risk of fever compared to children who received DTaP-containing control vaccine (i.e., without Hib vaccine). DTaP-IPV/Hib was not associated with any other medically-attended adverse health event.

Vaccine Storage and Handling

Hib vaccines should be maintained at refrigerator temperature between 2°C and 8°C (36°F and 46°F). Manufacturer package inserts contain additional information. For complete information on best practices and recommendations for vaccine storage and handling, please refer to CDC's *Vaccine Storage and Handling Toolkit*, www.cdc.gov/vaccines/hcp/admin/storage/toolkit/storage-handling-toolkit.pdf.

Surveillance and Reporting of Hib Disease

Reporting of *H. influenzae* varies by state. Invasive H. influenzae infections became nationally notifiable in 1991. Reporting of serotype information continues to be incomplete. For information on the case definition and guidance on case and contact investigations, please consult the Manual for the Surveillance of Vaccine-Preventable Diseases, www.cdc.gov/vaccines/pubs/surv-manual/index.html.

NOTES

Acknowledgements

The editors would like to acknowledge Elizabeth Briere, Susan Hariri, and Heidi Soeters for their contributions to this chapter.

Selected References

American Academy of Pediatrics. *Haemophilus influenzae* infections. In: Kimberlin D, Brady M, Jackson M, et al., eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:367–75.

Bisgard K, 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(2):229–37.

Blain A, MacNeil J, Wang X, et al. Invasive *Haemophilus influenzae* disease in adults ≥65 years, United States, 2011. *Open Forum Infect Dis* 2014;1(2):ofu044.

CDC. Prevention and Control of *Haemophilus influenzae* Type b Disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2014;63(No. RR-1):1–14.

CDC. Food and Drug Administration approval for use of Hiberix as a 3-Dose primary *Haemophilus influenzae* type b (Hib) vaccination series. *MMWR* 2016;65(16):418–9.

CDC. *Haemophilus influenzae* invasive disease among children aged <5 years—California, 1990–1996. *MMWR* 1998;47(35):737–40.

CDC. Prevention and Control of *Haemophilus influenzae* type b disease: recommendations of the ACIP, 2014. *MMWR* 2014;63 (RR-01):1–14.

CDC. Progress toward elimination of *Haemophilus influenzae* type b disease among infants and children—United States, 1998–2000. *MMWR* 2002;51(11):234–7.

Decker M, Edwards K. *Haemophilus influenzae* type b vaccines: history, choice and comparisons. *Pediatr Infect Dis* J 1998;17(9 Suppl):S113–6.

Livorsi D, MacNeil J, Cohn A, et al. Invasive *Haemophilus influenzae* in the United States, 1999–2008: epidemiology and outcomes. *J Infect* 2012;65(6):496–504.

MacNeil J, Cohn A, Farley M, et al. Current epidemiology and trends in invasive *Haemophilus influenzae* disease–United States, 1989–2008. *Clin Infect Dis* 2011;53(12):1230–6.

Nanduri S, Sutherland A, Gordon L, et al. *Haemophilus influenzae* vaccines. In: Plotkin S, Orenstein W, Offit P, et al., eds. *Plotkin's Vaccines*. 7th ed. Elsevier;2018:301–18.

Orenstein W, Hadler S, Wharton M. Trends in vaccine-preventable diseases. *Semin Pediatr Infect Dis* 1997;8(1):23–33.

Soeters H, Blain A, Pondo T, et al. Current epidemiology and trends in invasive *Haemophilus influenzae* disease — United States, 2009–2015. *Clin Infect Dis* 2018;67(6):881–9.

Hepatitis A

Monique A Foster, MD MPH; Penina Haber, MPH; Noele P Nelson, MD, PhD, MPH

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

Hepatitis A

- Descriptions of epidemic jaundice attributed to Hippocrates
- Differentiated from hepatitis B in 1940s
- Serologic tests developed in 1970s
- Vaccines first licensed in the U.S. in 1995

In the prevaccine era, the primary methods used for preventing hepatitis A were hygienic measures and passive protection with immune globulin (IG). Hepatitis A (HepA) vaccines were first licensed for use in the United States in 1995. These vaccines provide long-term protection against hepatitis A virus (HAV) infection. The similarities between the epidemiology of hepatitis A and poliomyelitis suggest that widespread vaccination of appropriate susceptible populations with HepA vaccines can substantially lower disease incidence, eliminate virus transmission, and ultimately, eliminate HAV infection. Prior to 2004, hepatitis A was the most frequently reported type of hepatitis in the United States. From 1996, when the HepA vaccine was introduced, through 2011, hepatitis A cases decreased by over 95%, but re-emerged in 2016 in the United States due to widespread outbreaks among persons reporting drug use and homelessness. In response, CDC has been assisting multiple state and local health departments with hepatitis A outbreaks.

Hepatitis A Virus

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

Hepatitis A Virus

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

Pathogenesis

HAV is typically acquired through ingestion (through fecal-oral transmission) and replicates in the liver. After 10 to 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

Hepatitis A Pathogenesis

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

begins to decline at the onset of clinical illness and decreases significantly by 7 to 10 days after onset of symptoms. Most infected persons no longer excrete virus in the feces by the third week of illness.

Hepatitis A Clinical Features

- Incubation period 28 days (range, 15 to 50 days)
- Symptoms: Abrupt onset of fever, malaise, anorexia, nausea, abdominal discomfort, dark urine, jaundice
- Likelihood of symptomatic illness directly related to age
- Children generally asymptomatic, adults symptomatic

Clinical Features

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

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

Complications

Severe clinical manifestations of hepatitis A infection are rare; however, atypical complications may occur, including immunologic, neurologic, hematologic, pancreatic, and renal manifestations. Relapsing hepatitis, cholestatic hepatitis A, hepatitis A triggering autoimmune hepatitis, subfulminant hepatitis, and fulminant hepatitis have also been reported. Fulminant hepatitis is the most severe rare complication, with mortality estimates up to 80%. Overall case-fatality estimates range from 0.3% to 0.6% for all ages and up to 1.8% among adults age 50 years or older. During outbreaks concentrated in older individuals or higher proportions of individuals with comorbidities, case-fatality rates can be significantly higher. Vaccination of high-risk groups and other public health measures have significantly reduced the overall number of hepatitis A cases and fulminant HAV infections. However, even nonfatal hepatitis A results in substantial morbidity, with associated costs of medical care and work loss.

Laboratory Testing

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

IgG anti-HAV appears in the convalescent phase of infection, remains present in serum for the lifetime of the person, and confers enduring protection against disease. The antibody test for total anti-HAV measures both IgG anti-HAV and IgM anti-HAV. Persons who are total anti-HAV-positive and IgM anti-HAV-negative have serologic markers indicating immunity consistent with either past infection or vaccination.

Molecular virology methods such as polymerase chain reaction (PCR)-based assays can be used to amplify and sequence viral genomes. These assays are helpful to investigate common-source outbreaks of hepatitis A.

Medical Management

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

Epidemiology

Occurrence

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

Reservoir

Humans are the only natural reservoir of the virus. There are no insect or animal vectors. A chronic HAV state has not been reported although infections may relapse or be prolonged.

Transmission

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

Temporal Pattern

There is no appreciable seasonal variation in hepatitis A incidence. In the prevaccine era, cyclic increases in reported acute cases were observed every 10 to 15 years and were characterized by large community outbreaks of disease.

Hepatitis A Epidemiology

- Reservoir
  - Human
- Transmission
  - Fecal-oral
- Temporal pattern
  - None
- Communicability
  - Most infectious 1-2 weeks before onset of illness

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 symptoms.

Risk Factors

Groups at increased risk for hepatitis A or its complications include international travelers (particularly those with high-risk itineraries such as travel to rural areas in high-risk regions [Central and South America, Africa, Asia]), recent international adoptees from hepatitis A-endemic countries and their contacts, men who have sex with men, people experiencing homelessness, persons with HIV, and people who use drugs. Outbreaks of hepatitis A have also been reported among persons working with hepatitis A–infected primates.

Persons with chronic liver disease are not at increased risk of infection but are at increased risk of developing fulminant hepatitis A if infected.

Persons with clotting factor disorders may be at increased risk of hepatitis A because of administration of solvent/detergent-treated factor VIII and IX concentrates; however, secondary virus reduction steps, common use of recombinant clotting factor concentrates, and screening of plasma for HAV has greatly reduced the risk of HAV transmission from clotting factors to the same as that among the general population.

Persons with occupational risk include only those who work with hepatitis A–infected nonhuman primates or with clinical or nonclinical material containing hepatitis A virus in a research laboratory setting. Food handlers are not at increased risk for hepatitis A because of their occupation, and secondary transmission from food handlers is rare. Health care personnel do not have an increased incidence 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. Other than the occasional transmission within health care settings, no worker-related HAV infections have been reported in the United States. Consistently, serologic studies in the United States have shown no or mildly increased risk of HAV infection in wastewater workers.

Historically, HAV infection was highly endemic in institutions for persons with developmental disabilities. Now, persons with developmental disabilities typically live in group homes or residential facilities. Outbreaks can occur in these settings. Schools are not common sites for HAV transmission. Multiple cases among children at a school require investigation to identify a common source and efforts to improve immunization coverage.

Children generally have asymptomatic or unrecognized illnesses, so they may serve as a source of infection, particularly for household or other close contacts.

In 2018, 5,026 (40%) of the 12,474 hepatitis A cases reported in the United States had a risk factor identified; the other 60% either had no risk factor identified or risk factor data were missing. Of the 40% with a risk factor identified, injection drug use was the most commonly identified risk factor. Other sources of infection identified in the United States in 2018 included men who have sex with men, sexual/household contact with a hepatitis-A-infected person, other contact with a hepatitis A patient, and international travel.

Secular Trends in the United States

Hepatitis A became nationally notifiable as a distinct entity in 1966. During the prevaccine era in the United States, hepatitis A occurred in large, nationwide epidemics. The largest number of cases reported in one year (59,606) was in 1971. Prior to 2000, the incidence of reported hepatitis A was substantially higher in the western United States than in other parts of the country. From 1987 to 1997, 11 mostly western states (Arizona, Alaska, Oregon, New Mexico, Utah, Washington, Oklahoma, South Dakota, Idaho, Nevada, California) accounted for 50% of reported cases, but only 22% of the U.S. population. Historically, children age 2 through 18 years had the highest rates of hepatitis A (15 to 20 cases per 100,000 population in the early to mid-1990s).

In 1996, CDC's Advisory Committee on Immunization Practices (ACIP) recommended administration of HepA vaccine to persons at increased risk for the disease, including international travelers, men who have sex with men, people who use non-injection and injection drugs, and children living in communities with high rates of disease. In 1999, ACIP also recommended routine vaccination for children living in 11 Western states with average hepatitis A rates of more than 20 cases per 100,000 population and recommended that vaccination be considered for children in an additional 6 states with rates of 10 to 20 cases per 100,000 population. ACIP expanded these recommendations in 2006 to include routine vaccination of children beginning at age 12 months in all 50 states. In 2019, the ACIP recommended vaccination of all persons experiencing homelessness age 1 year or older. In 2020, ACIP recommended vaccination of all children and adolescents age 2 through 18 years who have not previously received HepA vaccine and routine vaccination of all persons with HIV age 1 year or older.

Hepatitis A rates have been declining since vaccination initiation in 1996 and were less than 1 case per 100,000 until increases occurred due to widespread outbreaks among persons reporting drug use and homelessness. The number

Hepatitis A Secular Trends in the United States

- Large, nationwide epidemic during prevaccine era
- Historically, children 2–18 had highest rates of hepatitis A (15 to 20 cases per 100,000)
- Prior to 2000, incidence higher in Western states
- Rates declined 95.5% since vaccination initiation in 1996 to 2011
- From 2016-2021, over 37,000 outbreak-associated cases reported from 35 states

of reported acute hepatitis A cases decreased 95.5% overall from 1996 to 2011. Many of the high-incidence states began routine hepatitis A vaccination programs for children in the late 1990s, and since 2002, rates have been similar in all parts of the country, ranging from 0.1 case per 100,000 population to 5.1 cases per 100,000 population. Since 2002, rates among children have declined. The wider use of vaccine is largely responsible for the marked decrease in hepatitis A rates in the United States, for the elimination of regional disparities in rates of infection, and for decreased infection rates in children. Beginning in the late 1990s, national age-specific rates declined more rapidly among children than adults; rates were similar among all age groups until the widespread person-to-person outbreaks occurred in 2017, primarily impacting adults and increasing rates among individuals age 20 years or older. Historic differences in rates among racial/ethnic populations have narrowed in the vaccine era.

In 2018, 12,474 cases of acute hepatitis A were reported nationwide to CDC. The overall incidence rate for 2018 was 3.8 cases per 100,000 population, an increase from recent years. The rate was similar for males and females but increased for persons older than age 20 years. In the United States, there have been decreases in incidence of hepatitis A due to universal childhood vaccination. However, this has resulted in the average age of hepatitis A-related hospitalizations and deaths increasing, and the proportion of persons hospitalized is more likely to have liver diseases and other comorbid medical conditions. Analysis of anti-HAV positivity prevalence, based on data from the National Health and Nutrition Examination Surveys (NHANES) conducted in 2007–2016, showed a significant increase among children age 6 through 19 years, and significant increases occurred in the proportion of children age 6 to 19 years with immune markers of protection, most likely from vaccination. Minimal change in anti-HAV positivity prevalence occurred among adults age 20 through 39 years, with 74% of adults being susceptible to disease. Significant decreases occurred in the proportion of adults age 40 years or older with protection. During 2007–2016, the prevalence of anti-HAV positivity among U.S.-born residents differed significantly by race/ethnicity. Overall, antibody positivity prevalence was lowest among non-Hispanic whites, intermediate among non-Hispanic blacks, and greatest among Hispanics across all age groups.

During 2017, a total of 1,521 outbreak-associated HAV cases were reported from California, Kentucky, Michigan, and Utah, with 1,073 (71%) hospitalizations and 41 (3%) deaths; most infections were among persons reporting homelessness or injection or non-injection drug use. From August 2016 through January 2021, over 37,000 outbreak-associated cases had been reported from 35 states.

Among children born during 2016–2017, 85.8% had received at least 1 dose of HepA vaccine by age 24 months, an increase of 1.8 percentage points from 2014–2015. By age 35 months, 76.9% had received at least 2 doses of HepA vaccine, a 2.0 percentage point increase from 2014–2015. In 2019, 77.1%, of adolescents age 13-17 years had received at least 2 doses of HepA vaccine compared with 73.6% the year prior. For adults age 19 years or older, vaccination coverage in 2017 was reported at 10.9% for at least 2 doses.

Hepatitis A Vaccines

To produce HepA vaccines, cell culture–adapted virus is propagated in human fibroblasts, purified from cell lysates, inactivated with formalin, and adsorbed to an aluminum hydroxide adjuvant. Single-antigen HepA vaccine was licensed for use in the United States in 1995 (Havrix) and 1996 (Vaqta). In 2001, a combination HepA-HepB vaccine (Twinrix) was licensed.

Characteristics

Single-antigen HepA vaccines (Havrix and Vaqta) are available in two formulations: pediatric and adult. The pediatric formulations of Havrix and Vaqta contain 720 ELISA units and 25 HAV units per dose, respectively. The adult formulations of Havrix and Vaqta contain 1,440 ELISA units and 50 HAV units per dose, respectively. Twinrix contains 720 ELISA units of HepA vaccine and 20 micrograms of hepatitis B surface antigen protein per dose. HepA vaccines are administered by the intramuscular route.

Twinrix contains yeast protein. Each dose of HepA vaccine contains aluminum as an adjuvant and neomycin as an antibiotic. HepA vaccines contain no preservative. Presentations of HepA vaccines contain latex rubber.

Vaccination Schedule and Use

The pediatric formulations of Havrix and Vaqta vaccines are approved for persons age 12 months through 18 years. The adult formulations are approved for persons age 19 years or older. Both vaccines are approved as a 2-dose series. The second dose of Vaqta is administered 6 through 18 months after the first dose, and the second dose of Havrix is administered 6 through 12 months after the first dose.

HepA-HepB (Twinrix) is licensed for persons age 18 years or older and administered as a 3-dose series at 0, 1, and 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. Twinrix is approved for persons age 18 years or older and can be used in persons in this age group

Hepatitis A Vaccines

- HepA (Havrix, Vaqta)
- HepA-HepB (Twinrix)

Hepatitis A Vaccine Characteristics

- Administered by intramuscular injection
- Contains aluminum adjuvant and neomycin
- Twinrix contains yeast protein
- Some presentations contain latex rubber

Hepatitis A Vaccination Schedule

- All children age 12 through 23 months and all children and adolescents age 2 through 18 years who have not previously received HepA vaccine
  - 2-dose series at 0, 6–18 months (Vaqta)
  - 2-dose series at 0, 6–12 months (Havrix)
- Adults age 19 years or older with risk factors
  - 2-dose series at 0, 6–18 months (Vaqta)
  - 2-dose series at 0, 6–12 months (Havrix)
  - 3-dose series at 0, 1, 6 months (Twinrix)
  - 3-dose series with doses at 0, 7, 21–30 days, and booster 12 months after dose 1 (Twinrix, accelerated)

with indications for both hepatitis A and hepatitis B vaccines. Twinrix is also approved using an alternative schedule with doses at 0, 7, and 21–30 days and a booster dose 12 months after the first dose.

All children should receive hepatitis A vaccine at age 1 year (i.e., 12 through 23 months). Vaccination should be completed according to the licensed schedules. All children and adolescents age 2 through 18 years who have not previously received HepA vaccine should be vaccinated (i.e., children and adolescents are recommended for catch-up vaccination).

Adults age 19 years or older with risk factors should receive the adult formulation of HepA vaccine. Persons at increased risk for HAV infection, or who are at increased risk for severe disease from HAV infection, should be routinely vaccinated.

Immune Globulin

Immune globulin (IG) provides protection against hepatitis A through passive transfer of antibody. GamaSTAN is a sterile, preservative-free solution of IG for intramuscular administration and is used for prophylaxis against diseases caused by HAV, measles, varicella, and rubella viruses. GamaSTAN is the only IG product approved by FDA for hepatitis A prophylaxis. In 2017, the dosing of IG was changed to reflect decreased IgG anti-HAV potency, likely resulting from decreasing prevalence of previous HAV infection among plasma donors. GamaSTAN can be administered simultaneously with inactivated vaccines or toxoids in a different anatomic site (e.g., separate limbs) or at any time interval between doses. When MMR and varicella vaccines are recommended, they should be administered at least 2 weeks before or at least 6 months after the administration of IG.

Travelers

Persons at increased risk for hepatitis A should be identified and vaccinated. HepA vaccine is recommended for persons age 6 months or older traveling to or working in countries where they would have a high or intermediate endemicity of HAV infection. These persons should be vaccinated, or receive IG if too young or contraindicated for vaccine, before departure. For travelers who are partially vaccinated already (i.e., did not receive a full vaccine series), a dose should be administered before travel, if needed, according to the vaccine schedule. If the first dose was given within the past 6 months, a second dose is not needed before travel.

HepA vaccine should be administered to infants age 6 through 11 months traveling outside the United States when protection against HAV is recommended. The travel-related dose for infants age 6 through 11 months does not count toward the routine 2-dose series. Therefore, the 2-dose HepA vaccination series should be initiated at age 12 months with the appropriate dosage and schedule.

Healthy persons age 12 months through 40 years who are planning on traveling to an area with high or intermediate hepatitis A endemicity and who have not received HepA vaccine should receive a single dose of HepA vaccine as soon as travel is considered and should complete the HepA vaccine series with the appropriate dosage and schedule.

Persons older than age 40 years, persons with immunocompromising conditions, and persons with chronic liver disease planning on traveling to an area with high or intermediate HAV endemicity should receive a single dose of HepA vaccine as soon as travel is considered. Persons traveling in less than 2 weeks should receive the initial dose of HepA vaccine and simultaneously may be administered IG in a different anatomic injection site (e.g., separate limbs). The HepA vaccine series should be completed according to the routine schedule.

Travelers for whom vaccine is contraindicated, who choose not to receive HepA vaccine when it is indicated, and persons younger than age 6 months old should receive IG. Persons traveling for up to 1 month should receive a single dose of IG (0.1 mL/kg). Persons traveling for up to 2 months should receive IG at 0.2 mL/kg. Persons traveling for 2 months or longer should receive IG at 0.2 mL/kg repeated every 2 months for the duration of travel. Infants age <6 months traveling for 2 months or longer should receive IG at 0.2 mL/kg repeated every 2 months for the duration of travel or until the infant is administered HepA vaccine (i.e., at age ≥6 months).

International Adoptees and Persons Who Anticipate Close Personal Contact with an International Adoptee

Screening asymptomatic people for hepatitis A is generally not recommended; however, clinicians may decide to test internationally adopted children for anti-HAV IgG and IgM to identify those who may be acutely infected and shedding virus and to make decisions regarding HepA vaccination.

HepA vaccination is recommended for all previously unvaccinated persons who anticipate close personal contact (e.g., household contact or regular babysitting) with an international adoptee from a country of high or intermediate endemicity during the first 60 days following arrival of the adoptee in the United States. The first dose of the 2-dose HepA vaccine series should be administered as soon as adoption is planned, ideally 2 or more weeks before the arrival of the adoptee.

Vaccination of Groups at Increased Risk

- Persons age 6 months or older traveling to or working in countries with high or intermediate endemicity of HAV infection
  - <6 months or contraindicated for vaccine: IG
  - 6–11 months: 1 dose of HepA vaccine (does not count toward routine 2-dose series)
  - 12 months–40 years and partially vaccinated or unvaccinated: 1 dose of HepA vaccine
  - >40 years, immunocompromised, or chronic liver disease: 1 dose of HepA vaccine when travel is considered; if traveling in less than 2 weeks, 1 dose of HepA vaccine and may be administered IG in a separate limb
- International adoptees and persons who anticipate close personal contact with an international adoptee
  - Adoptees: Consider testing for anti-HAV IgG and IgM to guide decision-making
  - Contacts: 2-dose series as soon as adoption is planned
- Persons experiencing homelessness, persons with chronic liver disease, persons with HIV: Routine vaccination

Persons Experiencing Homelessness

All persons age 1 year or older experiencing homelessness should be routinely vaccinated against hepatitis A. HepA vaccine should be integrated into routine preventive services for persons experiencing homelessness. A homeless person is defined as an individual: who lacks housing (without regard to whether the individual is a member of a family), including an individual whose primary residence during the night is a supervised public or private facility (e.g., shelter) that provides temporary living accommodations and an individual who is a resident in transitional housing; without permanent housing who may live on the streets; stay in a shelter, mission, single-room occupancy facility, abandoned building or vehicle; or in any other unstable or nonpermanent situation; who is "doubled up," a term that refers to a situation where individuals are unable to maintain their housing situation and are forced to stay with a series of friends or extended family members.

Persons with Chronic Liver Disease

Persons with chronic liver disease are at increased risk for fulminant hepatitis A should they become infected. Persons who have chronic liver disease, including those who either are awaiting or have received liver transplantation, should be vaccinated. Persons with chronic liver disease (including but not limited to persons with hepatitis B virus infection, hepatitis C virus infection, cirrhosis, fatty liver disease, alcoholic liver disease, autoimmune hepatitis, or an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level persistently greater than twice the upper limit of normal) should be routinely vaccinated against hepatitis A.

Persons with HIV

All persons with HIV infection age 1 year or older should be routinely vaccinated with HepA vaccine. Because the response to the vaccine might be reduced in persons with HIV infection who are immunosuppressed, postvaccination serologic testing should be performed for all persons with HIV infection at least 1 month after completing the HepA vaccine series.

HepA vaccination is not routinely recommended for health care personnel, persons attending or working in child care centers, food service establishments and food handlers, or persons who work in liquid or solid waste management (e.g., sewer workers or plumbers). These persons have not been shown to be at increased risk for HAV infection. In addition, transmission of HAV from infected food handlers to susceptible consumers or restaurant patrons in the workplace is rare. As of 2020, persons who receive blood products for clotting disorders (e.g., hemophilia) are no longer specifically recommended to receive HepA vaccine.

Vaccine Interchangeability

Limited data indicate that vaccines from different manufacturers are interchangeable. Completion of the series with the same product is preferable. However, if the originally used product is not available or not known, vaccination with either product is acceptable.

For both vaccines, the dosage of the second dose should be based on the person's age at the time of the dose, not the age when the first dose was given. The minimum interval between the first and second doses of hepatitis A vaccine is 6 months. There is no maximum interval for either vaccine. A second dose given at 12 months or longer after the first dose need not be repeated.

Single-antigen hepatitis A and hepatitis B vaccines may be used in conjunction with Twinrix to form a complete series of these vaccines. Because the hepatitis B component of Twinrix is equivalent to a standard adult dose of hepatitis B vaccine, the schedule when vaccinating against hepatitis B is the same regardless of which hepatitis B vaccine (i.e., single-antigen or Twinrix) is used for which dose. Because the hepatitis A component of Twinrix is equivalent to a pediatric dose of hepatitis A vaccine, a series mixing the single-antigen hepatitis A vaccine and Twinrix is more complex. A person age 19 years or older who receives 1 dose of Twinrix may complete the hepatitis A series with 2 doses of adult formulation hepatitis A vaccine separated by at least 5 months. A person who receives 2 doses of Twinrix may complete the hepatitis A series with 1 dose of adult formulation hepatitis A vaccine 5 months after the second dose. A person who begins the hepatitis A series with single-antigen hepatitis A vaccine may complete the series with 2 doses of Twinrix or 1 dose of adult formulation hepatitis A vaccine. Persons age 18 years should follow the same schedule using the pediatric formulation.

Vaccination series for adult using a combination of single-antigen HepA vaccine and Twinrix

1st Dose	2nd Dose*	3rd Dose†
TWINRIX	TWINRIX	TWINRIX
		Single-Antigen
		[Not Needed]§
	Single-Antigen	TWINRIX
		Single-Antigen
		[Not Needed]§
Single-Antigen	TWINRIX	TWINRIX
		Single-Antigen
		[Not Needed]§
	Single-Antigen¶	[Not Needed]

Persons age 19 years and older—use adult formulation hepatitis A vaccine. Persons age 18 years old—use pediatric formulation hepatitis A vaccine.

*1 month after first dose (see § for exception)

†5 months after second dose

§A third dose is not needed if all three conditions are met: 1) person being vaccinated is not yet age 19 years old; 2) 6 months separate the first 2 doses; 3) protection against hepatitis B disease is NOT needed.

¶6 months after first dose

Postexposure Prophylaxis (PEP)

HepA vaccine should be administered as soon as possible, within 2 weeks of exposure, to all unvaccinated persons age 12 months or older who have recently been exposed to HAV. In addition to HepA vaccine, coadministration of IG (0.1 mL/kg) is recommended under certain circumstances and for persons age 40 years or older based on the provider's risk assessment. Considerations regarding decision to use IG, vaccine, or both should include the ability of the person to develop a protective level of antibodies after receipt of HepA vaccine, the magnitude of the risk for HAV transmission from the exposure, and the availability of IG and vaccine.

Unvaccinated persons who are immunocompromised or have chronic liver disease and who have been exposed to HAV within the past 14 days should receive both IG (0.1 mL/kg) and HepA vaccine simultaneously in a different anatomic site (e.g., separate limbs) as soon as possible after exposure.

When the dose of HepA vaccine administered for postexposure prophylaxis is the first dose the exposed person has received, a second dose should be administered 6 months after the first for long-term immunity; however, the second dose is not necessary for PEP.

IG (0.1 mL/kg) is recommended for postexposure prophylaxis for children younger than age 12 months and for persons for whom vaccine is contraindicated.

Immunogenicity and Vaccine Efficacy

Both monovalent HepA vaccines are highly immunogenic. More than 95% of adults will develop protective antibody within 4 weeks of a single dose of either vaccine, and nearly 100% will seroconvert after receiving 2 doses. Among children and adolescents, more than 97% will be seropositive within a month of the first dose. In clinical trials, all recipients aged 2–18 years had protective levels of antibody after 2 doses.

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

The exact duration of protection after vaccination is unknown. Anti-HAV has been shown to persist for at least 25 years in adults administered inactivated vaccine as children with the 3-dose schedule recommended prior to 1999, and anti-HAV persistence of at least 20 years also was demonstrated among persons vaccinated with a 2-dose schedule as adults. Detectable antibodies are estimated to persist for 40 years or longer based on mathematical modeling and anti-HAV kinetic studies.

Hepatitis A Vaccine Efficacy

- Highly immunogenic
- More than 95% of adults develop protective antibody within 4 weeks of a single dose
- More than 97% of children and adolescents will be seropositive within 1 month of the first dose

Contraindications and Precautions to Vaccination

As with other vaccines, a history of a severe allergic reaction (anaphylaxis) to a vaccine component or following a prior dose is a contraindication to further doses. Moderate or severe acute illness (with or without fever) in a patient is considered a precaution to vaccination, although persons with minor illness may be vaccinated.

Contraindications to Twinrix include the contraindications to HepB vaccine.

Hepatitis A Vaccine Contraindications and Precautions

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

Vaccine Safety

The most frequently reported adverse events to the Vaccine Adverse Event Reporting System (VAERS) for single-antigen hepatitis A vaccines were fever, injection site erythema, injection site swelling, and rash. The most frequently reported adverse events for combination hepatitis A vaccine and hepatitis B vaccine were fever, headache, injection site pain, and dizziness.

Hepatitis A Vaccine Safety

- Single-antigen HepA vaccines: Fever, injection site erythema, injection site swelling, rash
- HepA-HepB vaccine: Fever, headache, injection site pain, dizziness

Vaccination in Pregnancy

A review of VAERS did not identify any concerning patterns of adverse events in pregnant women or their infants after vaccination with Havrix, Vaqta, or Twinrix during pregnancy. A multisite study in CDC's Vaccine Safety Datalink (VSD) of maternal HepA vaccination found that HepA vaccine administration during pregnancy was not associated with increased risk for a range of adverse events examined among pregnancies resulting in live births. However, an association was found between maternal HepA vaccination and infants who were small for gestational age. Investigators believe this association was likely due to unmeasured confounding but might warrant additional consideration.

Vaccine Storage and Handling

HepA vaccines should be maintained at refrigerator temperature between 2°C and 8°C (36°F and 46°F). Manufacturer package inserts contain additional information. For complete information on best practices and recommendations, please refer to CDC's Vaccine Storage and Handling Toolkit, www.cdc.gov/vaccines/hcp/admin/storage/toolkit/storage-handling-toolkit.pdf.

Surveillance and Reporting for Hepatitis A

The 2019 Council of State and Territorial Epidemiologists surveillance case definition for hepatitis A clinical criteria includes an acute illness with a discrete onset of any sign or symptom consistent with acute viral hepatitis (e.g., fever, headache, malaise, anorexia, nausea, vomiting, diarrhea, and abdominal pain), and either a) jaundice or elevated bilirubin levels greater than or equal to 3 mg/dL, or b) elevated serum ALT levels greater than 200 IU/L and the absence of a more likely diagnosis. Since hepatitis A cannot be differentiated from other types of viral hepatitis on clinical or epidemiologic features alone, serologic evidence of HAV infection or detection of HAV through nucleic acid testing is necessary. The laboratory criteria for hepatitis A requires the presence of HAV-specific IgM antibody or a positive nucleic acid amplification test. For additional information on the case definition and guidance on case and contact investigations, please consult the Manual for the Surveillance of Vaccine-Preventable Diseases, www.cdc.gov/vaccines/pubs/surv-manual/index.html.

Acknowledgements

The editors would like to acknowledge Clive Brown, Maria Cano, and Jennifer Hamborsky for their contributions to this chapter.

Selected References

Acheson D, Fiore A. Hepatitis A transmitted by food. *Clin Infect Dis* 2004;38(5):705–15.

Ajmera V, Xia G, Vaughan G, et al. What factors determine the severity of hepatitis A-related acute liver failure? *J Viral Hepat* 2011;18(7):e167–74.

Averhoff F, Khudyakov Y, Nelson N, et al. In: Plotkin S, Orenstein W, Offit P, et al., eds. *Plotkin's Vaccines*. 7th ed. Philadelphia, PA: Elsevier;2018:319–41.

Barrett C, Pape B, Benedict K, et al. Impact of Public Health Interventions on Drinking Water-Associated Outbreaks of Hepatitis A - United States, 1971-2017. *MMWR* Morb Mortal Wkly Rep. 2019 Sep 6;68(35):766–70. doi: 10.15585/mmwr.mm6835a4.

Bergeisen G, Hinds M, Skaggs J. A waterborne outbreak of hepatitis A in Meade County, Kentucky. *Am J Public Health* 1985;75(2):161–4.

Bloch A, Stramer S, Smith J, et. al. Recovery of hepatitis A virus from a water supply responsible for a common source outbreak of hepatitis A. *Am J Public Health* 1990;80(4):428–30.

Bowen G, McCarthy M. Hepatitis A associated with a hardware store water fountain and a contaminated well in Lancaster County, Pennsylvania, 1980. *Am J Epidemiol* 1983;117(6):695–705.

Bryan J, Henry C, Hoffman A, et. al. Randomized, cross-over, controlled comparison of two inactivated hepatitis A vaccines. *Vaccine* 2000;19(7-8):743–50.

CDC. Hepatitis A outbreak associated with green onions at a restaurant—Monaca, Pennsylvania, 2003. *MMWR* 2003;52(47):1155–7.

CDC. Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2006;55(RR07):1–23.

CDC. Prevention of hepatitis A virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices, 2020. *MMWR* 2020;69(5);1–38.

NOTES

NOTES

CDC. Update: recommendations of the Advisory Committee on Immunization Practices for use of hepatitis A vaccine for postexposure prophylaxis and for preexposure prophylaxis for international travel. *MMWR* 2018;67(43):1216–1220.

CDC. Updated Recommendations from the Advisory Committee on Immunization Practices (ACIP) for Use of Hepatitis A Vaccine in Close Contacts of Newly Arriving International Adoptees. *MMWR* 2009;58(36);1006–7.

CDC. Viral Hepatitis Surveillance – United States, 2018. https://www.cdc.gov/hepatitis/statistics/2018surveillance/HepA.htm. Accessed January 15, 2021.

Collier M, Khudyakov Y, Selvage D, et. al. Outbreak of hepatitis A in the USA associated with frozen pomegranate arils imported from Turkey: an epidemiological case study. *Lancet Infect Dis* 2014;14(10):976–81.

Collier M, Tong X, Xu F. Hepatitis A hospitalizations in the United States, 2002–2011. *Hepatology* 2014;61(2):481–5.

Council of State and Territorial Epidemiologists. National Notifiable Diseases Surveillance System (NNDSS), Hepatitis A, Acute, 2019 Case Definition. (https://wwwn.cdc.gov/nndss/conditions/hepatitis-a-acute/case-definition/2019. Accessed December 14, 2019).

De Serres G, Cromeans T, Levesque B, et. al. Molecular confirmation of hepatitis A virus from well water: epidemiology and public health implications. *J Infect Dis* 1999;179(1):37–43.

Epson E, Cronquist A, Lamba K, et. al. Risk factors for hospitalisation and associated costs among patients with hepatitis A associated with imported pomegranate arils, United States, 2013. *Public Health*. 2016 Jul;136:144–51. doi: 10.1016/j.puhe.2016.03.27.

USFDA. Vaccines licensed for use in the United States. Silver Spring, MD: US Food and Drug Administration. https://www.fda.gov/vaccines-blood-biologics/vaccines/vaccines-licensed-use-united-states. Accessed May 5, 2021.

Foster M, Ramachandran S, Myatt K, et al. Hepatitis A Virus Outbreaks Associated with Drug Use and Homelessness - California, Kentucky, Michigan, and Utah, 2017. *MMWR Morb Mortal Wkly Rep*. 2018 Nov 2;67(43):1208–10. doi: 10.15585/mmwr.mm6743a3.

Foster M, Hofmeister M, Kupronis B, et al. Increase in Hepatitis A Virus Infections - United States, 2013-2018. *MMWR Morb Mortal Wkly Rep.* 2019 May 10;68(18):413–5. doi: 10.15585/mmwr.mm6818a2.

Groom H, Smith N, Irving S, et al. Uptake and safety of hepatitis A vaccination during pregnancy: a Vaccine Safety Datalink study. *Vaccine* 2019;37:6648–55. https://doi.org/10.1016/j.vaccine.2019.09.043

Hens N, Habteab Ghebretinsae A, Hardt K, et al. Model based estimates of long-term persistence of inactivated hepatitis A vaccine-induced antibodies in adults. *Vaccine* 2014;32(13):1507–13.

Hill H, Yankey D, Elam-Evans L, et al. Vaccination Coverage by Age 24 Months Among Children Born in 2016 and 2017 - National Immunization Survey-Child, United States, 2017-2019. *MMWR Morb Mortal Wkly Rep.* 2020 Oct 23;69(42):1505-1511. doi: 10.15585/mmwr.mm6942a1.Hofmeister MG, Foster MA, Montgomery MP, et al. Notes from the Field: Assessing the Role of Food Handlers in Hepatitis A Virus Transmission - Multiple States, 2016-2019. *MMWR Morb Mortal Wkly Rep*. 2020 May 22;69(20):636–7. doi: 10.15585/mmwr.mm6920a4.

Hofmeister M, Xing J, Foster M, et al. Hepatitis A person-to-person outbreaks: Epidemiology, morbidity burden, and factors associated with hospitalization - Multiple States, 2016-2019. *J Infect Dis.* 2020 Oct 24:jiaa636. doi: 10.1093/infdis/jiaa636. Online ahead of print.

Hofmeister M, Yin S, Aslam M, et al. Hepatitis A Hospitalization Costs, United States, 2017. *Emerg Infect Dis*. 2020 May;26(5):1040–1.

Klevens R, Kruszon-Moran D, Wasley A, et al. Seroprevalence of hepatitis A virus antibodies in the U.S.: results from the National Health and Nutrition Examination Survey. *Public Health Rep* 2011;126(4):522–32.

Ly K, Klevens R. Trends in disease and complications of hepatitis A virus infection in the United States, 1999–2011: a new concern for adults. *J Infect Dis* 2015;212(2):176–82.

Morey R, Collier M, Nelson N. The financial burden of public health responses to hepatitis A cases among food handlers, 2012-2014. *Public Health Rep* 2017;132(4):443–7.

Moro P, Museru O, Niu M, et al. Reports to the Vaccine Adverse Event Reporting System after hepatitis A and hepatitis AB vaccines in pregnant women. *Am J Obstet Gynecol* 2014;210(6):561.e1-6.

NOTES

NOTES

Mosites E, Gounder P, Snowball M, et al. Hepatitis A vaccine immune response 22 years after vaccination. *J Med Virol*. 2018;90(8):1418–22.

Murphy T, Denniston M, Hill H, et. al. Progress toward eliminating hepatitis A disease in the United States. *MMWR* Suppl 2016;65(1):29–41.

Nelson N. Updated dosing Instructions for immune globulin (human) GamaSTAN S/D for hepatitis A virus prophylaxis. *MMWR* 2017;66(36):959–60.

Plumb I, Bulkow L, Bruce M, et. al. Persistence of antibody to hepatitis A virus 20 years after receipt of hepatitis A vaccine in Alaska. *J Viral Hepat* 2017:24(7):608–12.

Ramaswamy M, Bruden D, Nolen L, et al. Hepatitis A vaccine immunogenicity 25 years after vaccination in Alaska. *J Med Virol*. 2020 Jul 22.

Spada E, Genovese D, Tosti M, et. al. An outbreak of hepatitis A virus infection with a high case-fatality rate among injecting drug users. *J Hepatol* 2005;43(6):958–64.

Taylor R, Davern T, Munoz S, et al. US Acute Liver Failure Study Group. Fulminant hepatitis A virus infection in the United States: Incidence, prognosis, and outcomes. *Hepatology* 2006;44(6):1589–97.

Tejada-Strop A, Costafreda M, Dimitrova Z, et al. Evaluation of potencies of immune globulin products against hepatitis *JAMA Intern Med* 2017;177(3):430–2.

Theeten H, Van Herck K, Van Der Meeren O, et al. Long-term antibody persistence after vaccination with a 2-dose Havrix™ (inactivated hepatitis A vaccine): 20 years of observed data, and long-term model-based predictions. *Vaccine* 2015:33(42):5723–7.

Weldon M, VanEgdom M, Hendricks K, et al. Prevalence of antibody to hepatitis A virus in drinking water workers and wastewater workers in Texas from 1996 to 1997. *J Occup Environ Med* 2000:42(8):821–6.

Yin S, Barker L, Ly K, et al. Susceptibility to Hepatitis A Virus Infection in the United States, 2007-2016. *Clin Infect Dis.* 2020 Mar 20:ciaa298. doi: 10.1093/cid/ciaa298. Online ahead of print.

Penina Haber, MPH and Sarah Schillie, MD, MPH, MBA

Viral hepatitis is a term commonly used for several diseases that are clinically similar but etiologically and epidemiologically distinct. 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. Hepatitis D, or 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 are thought to be those that followed the administration of smallpox vaccine containing human lymph to shipyard workers in Germany in 1883. In the early and middle parts of the 20th century, serum hepatitis was repeatedly observed following the use of contaminated needles and syringes. The role of blood as a vehicle for virus transmission was further emphasized in 1943, when Paul Beeson described jaundice that had occurred in seven recipients of blood transfusions. Australia antigen, later called hepatitis B surface antigen (HBsAg), was first described in 1965, and the Dane particle (complete hepatitis B virion) was identified in 1970. Identification of serologic markers for HBV infection followed and helped to clarify the natural history of the disease. Ultimately, HBsAg, the surface protein of HBV, was manufactured in quantity and now comprises the immunogen in highly effective vaccines for prevention of HBV infection.

A plasma-derived Hepatitis B (HepB) vaccine was first licensed for use in the United States in 1981. The vaccine was safe and effective but was not well accepted, possibly because of unsubstantiated fears of transmission of live HBV and other blood-borne pathogens. Recombinant HepB vaccines replaced plasma-derived HepB vaccines beginning in 1986. Plasma-derived HepB vaccines are no longer used in the United States.

Hepatitis B

- Epidemic jaundice described by Hippocrates in 5th century BCE
- First recorded cases in 1883 following administration of smallpox vaccine containing human lymph
- Transmission via blood further emphasized in 1943
- HBsAg first described in 1965
- Plasma-derived HepB vaccine licensed in 1981 replaced in 1986 with recombinant HepB vaccines

Hepatitis B Virus (HBV)

HBV is a small, double-stranded DNA virus in the family Hepadnaviridae. Serologic markers for HBV infection include HBsAg, antibody to HBsAg (anti-HBs), immunoglobulin class M (IgM) antibodies to hepatitis B core antigen (IgM anti-HBc), and immunoglobulin class G (IgG) anti-HBc (IgG anti-HBc). At least one serologic marker is present during the different phases of infection. Hepatitis B e antigen (HBeAg) can be detected in persons with acute or chronic HBV infection; the presence of HBeAg correlates with viral replication, high viral levels of HBV DNA, and high infectivity; antibody to HBeAg (anti-HBe) usually correlates with the decrease of replicating virus, although reversion to HBeAg positivity can occur.

Hepatitis B Virus

- Hepadnaviridae family (DNA)
- Multiple serologic markers for infection
- Classified by serologic subtype and genotype, which vary geographically
- Infectious for at least 7 days on surfaces

HBV has been classified by two separate systems: serologic subtype and genotype. Nine serologic subtypes based on the heterogeneity of HBsAg have been described. Ten HBV genotypes, designated A through J, have been described. HBV serotypes and genotypes vary geographically. HBV genotypes are associated with the modes of HBV transmission (vertical versus horizontal) and with the risk of certain outcomes of chronic infection, such as cirrhosis and hepatocellular carcinoma (HCC). For example, in Alaska, HBV genotype F is associated with HCC in children as well as adults younger than age 30 years, while in Asia as well as Alaska, HBV genotype C has been associated with a significantly higher risk of HCC than other genotypes. Infection or immunization with one HBV genotype generally confers immunity to all genotypes.

HBV remains infectious for at least 7 days on environmental surfaces and is transmissible in the absence of visible blood.

Hepatitis B Pathogenesis

- Transmission by parenteral or mucosal exposure
- Replicates in hepatocytes
- Unique reverse transcription replication

Pathogenesis

HBV is transmitted by parenteral or mucosal exposure to HBsAg-positive body fluids from persons who have acute or chronic HBV infection. It replicates in hepatocytes through a unique reverse transcription process.

Hepatitis B Clinical Features

- Incubation period 60 to 90 days
- Clinical signs and symptoms more common in adults
- Prodromal phase lasts 3 to 10 days; abrupt onset of fever, malaise, anorexia, nausea, abdominal discomfort, and dark urine before jaundice
- Icteric phase lasts 1 to 3 weeks; jaundice, light or gray stools, hepatic tenderness, hepatomegaly
- Convalescent phase lasts weeks to months; malaise and fatigue persist while jaundice, anorexia, and other symptoms disappear
- Most adults recover while most infants progress to chronic infection

Clinical Features

The clinical course of acute hepatitis B is indistinguishable from that of other types of acute viral hepatitis. The incubation period typically ranges from 60 to 90 days. Clinical signs and symptoms occur more often in adults than in infants or children; infants and young children usually are asymptomatic. Approximately 50% of adults who have acute infections are asymptomatic.

The preicteric, or prodromal, phase from initial symptoms to onset of jaundice usually lasts 3 to 10 days. It is nonspecific and is characterized by abrupt onset of fever, malaise, anorexia, nausea, abdominal discomfort, and dark urine beginning 1 to 2 days before the onset of jaundice. The icteric phase is variable but usually lasts from 1 to 3 weeks and is characterized by jaundice, light or gray stools, hepatic tenderness, and hepatomegaly (splenomegaly is less common). During convalescence, malaise and fatigue may persist for weeks or months, while jaundice, anorexia, and other symptoms disappear.

Most acute HBV infections in adults result in complete recovery with elimination of HBsAg from the blood and the production of anti-HBs, creating immunity to future infection. In contrast, as many as 90% of HBV infections in infants progress to chronic infection. Perinatal transmission from mother to infant at birth (vertical transmission) is highly efficient. Prior to the widespread availability of postexposure prophylaxis,

the proportion of infants born to HBsAg-positive women that acquired HBV infection was approximately 30% for those born to HBeAg-negative mothers and 85% for those born to HBeAg-positive mothers. With postexposure prophylaxis, comprised of HepB vaccine and hepatitis B immune globulin (HBIG) at birth, followed by completion of the HepB vaccine series, 0.7% through 1.1% of infants develop infection; infants born to mothers with high viral loads are at greatest risk for infection despite receipt of HepB vaccine and HBIG.

Complications

While most acute HBV infections in adults result in complete recovery, fulminant hepatitis occurs in about 1% to 2% of acutely infected persons. Although the consequences of acute HBV infection can be severe, most of the serious complications associated with HBV infection are due to chronic infection.

Hepatitis B Complications

- Fulminant hepatitis in about 1% to 2% of acutely infected adults

Chronic HBV Infection

The proportion of persons with acute HBV infection who progress to chronic infection varies with age and immune status. As many as 90% of infants who acquire HBV infection from their mothers at birth or in infancy become chronically infected. Of children who become infected with HBV between age 1 and 5 years, 30% to 50% become chronically infected. The risk of acquiring chronic HBV infection when infected during adulthood is approximately 5%. Acute HBV progresses to chronic HBV in approximately 40% of hemodialysis patients and up to 20% of patients with immune deficiencies.

Chronic Hepatitis B Virus Infection (HBV)

- Proportion of persons with acute HBV that progress to chronic HBV
  - As many as 90% of infants
  - 30% to 50% of children between age 1 and 5 years
  - 5% of adults
- Often asymptomatic
- Responsible for most HBV-related morbidity and mortality
- 25% of persons infected as children and 15% of persons infected as adults will die prematurely

Persons with chronic infection are often asymptomatic and may not be aware they are infected; however, they are capable of infecting others and have been referred to as carriers. Chronic infection is responsible for most HBV-related morbidity and mortality, including chronic hepatitis, cirrhosis, liver failure, and HCC. Approximately 25% of persons who become chronically infected during childhood and 15% of those who become chronically infected after childhood will die prematurely from cirrhosis or liver cancer.

An estimated 257 million persons worldwide are living with HBV infection. HBV infection is an established cause of acute and chronic hepatitis and cirrhosis. The frequency of infection and patterns of transmission vary in different parts of the world. 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 has chronic HBV infection. In these high-prevalence areas, most infections are acquired at birth or during early childhood when the risk of developing chronic infections is greatest. In these areas, because most infections are asymptomatic, very little acute disease related to HBV occurs, but rates of chronic liver disease and liver cancer among adults are very high. In the United States, Western Europe, and

Australia, HBV infection is a disease of low endemicity. Infection occurs primarily during adulthood, and only 0.1% to 0.5% of the population has chronic HBV infection.

Laboratory Testing

Diagnosis is based on clinical, laboratory, and epidemiologic findings. HBV infection cannot be differentiated based on 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 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. The presence of HBsAg indicates that a person is infectious, regardless of whether the infection is acute or chronic. Transient HBsAg positivity can occur up to 18 days following vaccination (up to 52 days among hemodialysis patients) and is clinically insignificant.

Anti-HBs is a protective, neutralizing antibody. The presence of anti-HBs following acute HBV infection generally indicates recovery and immunity against reinfection. Anti-HBs can also be acquired as an immune response to HepB vaccine or passively transferred by administration of HBIG. The level of anti-HBs considered as a protective level of immunity when following a complete vaccination series is 10 mIU/mL. Persons who recover from natural HBV infection are typically positive for both anti-HBs and anti-HBc, whereas persons who respond to HepB vaccine are positive only for anti-HBs.

Anti-HBc 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 generally persists for life. Persons who are HBsAg-negative and anti-HBc-positive can experience reactivation of infection during chemotherapy or immunosuppressive therapy, with reappearance of HBsAg.

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.

HBeAg is a marker that is associated with a high number of infective HBV particles in the serum and a higher risk of infectivity. Anti-HBe correlates with a reduction of replicating virus and lower infectivity, although reversion to HBeAg positivity can occur.

HBV DNA assays are used to monitor response to treatment, assess the likelihood of perinatal HBV transmission, and detect the presence of occult HBV infection (i.e., infection in someone

who tests HBsAg-negative). In resource-limited settings, HBeAg may replace the use of HBV DNA for some purposes, e.g., assessment of perinatal HBV transmission risk.

Medical Management

There is no specific therapy for acute HBV infection. Treatment is supportive. Guidelines for management of chronic HBV infection in children and adults, including disease monitoring and antiviral therapy, are available from the American Association for the Study of Liver Diseases (AASLD, https://www.AASLD.org). Antiviral therapy, while not curative, can reduce the level of HBV DNA and quiet liver inflammation. Following the AASLD Guidelines/Guidance, antiviral therapy should generally be initiated in patients with chronic HBV infection who have high levels of virus and active liver inflammation characterized by elevated liver transaminase levels. These persons are at high risk for liver-related morbidity.

AASLD suggests antiviral therapy to reduce perinatal HBV transmission when maternal HBV DNA is greater than 200,000 IU/mL starting in the third trimester. Maternal therapy is generally discontinued at birth to 3 months postpartum.

Persons with acute or chronic HBV infections should prevent their blood and other potentially infective body fluids from contacting other persons. They should not donate blood or share toothbrushes or razors with household members. In health care settings, patients with HBV infection should be managed with standard precautions.

Epidemiology

Occurrence

HBV infection occurs worldwide. The frequency of infection varies in different parts of the world but is more common in some countries in Asia, Africa, South America, and the Caribbean.

Reservoir

HBV infection affects humans. Additionally, some primates (chimpanzee, gorilla, orangutan, gibbon) in Africa and Southeast Asia are infected with HBV.

Transmission

HBV is transmitted by parenteral or mucosal exposure to HBsAg-positive body fluids from persons who have acute or chronic HBV infection. The highest concentrations of virus are in blood and serous fluids; lower titers are found in other fluids, such as saliva, tears, urine, and semen. Semen is a vehicle for sexual transmission and saliva can be a vehicle of transmission through bites; other types of exposure (e.g., to saliva through kissing) are unlikely modes of transmission. HBsAg is also found

Hepatitis B Epidemiology

- Reservoir
  - Human
  - Some primates
- Transmission
  - Body fluids (highest concentration in blood and serous fluids)
- Temporal Pattern
  - No temporal pattern
- Communicability
  - Persons with acute or chronic HBV infection are infectious any time HBsAg present in blood
  - Persons with acute HBV infection can have HBsAg in blood 1–2 months before and after onset of symptoms

in other body fluids (e.g., breast milk, bile, feces, nasopharyngeal washings, and sweat). However, most body fluids are not efficient vehicles of transmission (unless they contain blood) because they contain low quantities of infectious HBV.

In the United States, the most important routes of transmission are injection-drug use, perinatal, and sexual contact with an infected person. Fecal-oral transmission does not appear to occur. However, transmission occurs among men who have sex with men (MSM), possibly via contamination from asymptomatic rectal mucosal lesions. In the 2000s and 2010s, outbreaks of hepatitis B occurred in long-term care facilities (e.g., assisted living facilities and nursing homes) as the result of inadequate infection control practices related to blood glucose monitoring. Transmission occurs in households from persons who have immigrated from endemic areas and who have chronic HBV infection.

Temporal Pattern

HBV infection is reported throughout the year. There is no known temporal pattern.

Communicability

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

Direct, percutaneous inoculation of HBV by needles during injection-drug use is an important mode of transmission. 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. Exposures such as transfusion of blood or blood products, hemodialysis, use of meters and lancets for blood glucose monitoring, insulin pens, and needle-stick or other sharps injuries sustained by health care personnel (HCP) have all resulted in HBV transmission. Outbreaks have been reported among patients in dialysis centers in many countries through failure to adhere to recommended infection control practices. Past outbreaks have been traced to tattoo parlors, acupuncturists, and barbers.

Hepatitis B Secular Trends in the United States

- Acute HBV infection
  - Before vaccine, about 9.6 per 100,000 cases
  - Following vaccine, about 1 per 100,000 cases in 2018 (~90% decrease)
  - During 2009 through 2013, KY, TN, and WV experienced 114% increase associated with injection-drug use
  - Incidence greatest for persons 40 through 49 years and lowest for persons 19 years or younger
- Chronic HBV infection
  - Estimated 850,000 to 2.2 million persons infected in the U.S.; most immigrated from endemic countries

Secular Trends in the United States

Hepatitis B became nationally notifiable as a distinct entity during the 1970s after serologic tests to differentiate different types of hepatitis became widely available.

In 2018, a total of 3,322 cases of acute hepatitis B were reported to CDC, for an overall incidence rate of 1.0 cases per 100,000 population. After adjusting for under-ascertainment and

under-reporting, an estimated 21,600 acute hepatitis B cases occurred in 2018. The rate of reported acute HBV infections declined approximately 90% since recommendations for HepB vaccination were first issued, from 9.6 cases per 100,000 population in 1982 to 1.0 cases per 100,000 population in 2018.

During 2009 through 2013, the combined incidence of acute HBV infection in three states (Kentucky, Tennessee, and West Virginia) increased 114% and was associated with increasing injection-drug use. Incidence is greatest for persons age 40 through 49 years (2.5 per 100,000 population); persons age 19 years or younger have the lowest incidence (0.02 cases per 100,000 population), likely a result of routine infant vaccination.

Although HBV infection is uncommon among adults in the general population (the lifetime risk of infection is less than 20%), it is highly prevalent in certain groups. Generally, the highest risk for HBV infection is associated with lifestyles, occupations, or environments in which contact with blood from infected persons is frequent. Chronic HBV infection has been identified in 3.5% to 20.0% of persons who inject drugs (PWID) in a variety of settings, and 22.6% of PWID have evidence of past infection.

An estimated 850,000 to 2.2 million persons in the United States are chronically infected with HBV. Most persons in the United States with chronic HBV infection have immigrated from endemic countries in the world. While screening persons who immigrate for HBsAg, anti-HBc and anti-HBs is recommended, it is not enforced. Therefore, clinicians and public health workers should screen all persons born in countries with high endemicity of HBV virus.

Among children born during 2015–2016, 75.0% received the HepB vaccine birth dose administered from birth through age 3 days. This was an increase from 71.8% for children born during 2013–2014. By age 24 months, 91.0% of children had received at least 3 doses of HepB vaccine. In 2017, 25.8% of adults age 19 years or older had received at least 3 doses of HepB vaccine; the coverage was 34.3% and 16.6% for adults age 19 through 49 years and age 50 years or older, respectively. Among HCP with direct patient contact, 70% had received at least 3 doses of HepB vaccine.

Hepatitis B Prevention Strategies

HepB vaccination is the mainstay of hepatitis B prevention efforts. A comprehensive strategy to eliminate HBV transmission includes universal vaccination of infants beginning at birth, routine vaccination of previously unvaccinated children less than age 19 years, and vaccination of adults at risk for HBV infection, including those requesting

protection from HBV without acknowledgement of a specific risk factor. It also includes universal testing of pregnant women for HBsAg to identify newborns who require immunoprophylaxis for prevention of perinatal infection and to pregnant women who can benefit from antiviral therapy to reduce perinatal transmission.

Hepatitis B Vaccines

- DTaP-HepB-IPV (Pediarix)
- DTaP-IPV-Hib-HepB (Vaxelis)
- HepA-HepB (Twinrix)
- HepB (Engerix-B, Heplisav-B, and Recombivax HB)

Hepatitis B Vaccine

The first recombinant HepB vaccine, Recombivax HB, was licensed in the United States in 1986. A second recombinant vaccine, Engerix-B, was licensed in 1989. Recombivax HB and Engerix-B are available in both pediatric and adult formulations. A third recombinant vaccine with a novel adjuvant, Heplisav-B, was licensed in 2017 for use in adults age 18 years or older. 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.

There are two combination vaccines that contain HepB vaccine. DTaP-HepB-IPV (Pediarix) is licensed for children age 6 weeks through 6 years. HepA-HepB (Twinrix) is licensed for persons age 18 years or older. A third combination vaccine, DTaP-IPV-Hib-HepB (Vaxelis), is licensed in the United States.

Hepatitis B Vaccine Characteristics

- Administered by intramuscular injection
- Contain yeast protein
- Contain aluminum adjuvant (Engerix-B and Recombivax HB) or synthetic adjuvant (Heplisav-B)
- Some presentations contain latex
- Ingredients in combination vaccines differ; all contain antibiotics

Characteristics

Recombinant HepB vaccine is produced by inserting a plasmid containing the gene for HBsAg into yeast (*Saccharomyces cerevisiae* or *Hansenula polymorpha*); HepB vaccines contain yeast protein. HepB vaccines are administered by intramuscular injection. Each dose of HepB vaccine contains aluminum as an adjuvant or, for Heplisav-B, a small synthetic immunostimulatory oligodeoxynucleotide 1018 adjuvant. Each dose of DTaP-HepB-IPV contains antibiotics neomycin and polymyxin B; each dose of DTaP-IPV-Hib-HepB contains neomycin, polymyxin B, and streptomycin; each dose of HepA-HepB contains neomycin. HepB vaccines contain no preservative. Presentations of HepB vaccines contain latex rubber. Specific ingredients in combination vaccines containing HepB vaccine differ.

Recombivax HB and Engerix-B are available in both pediatric and adult formulations and are typically administered as a 3-dose series on a 0, 1, 6 month schedule. Although their antigen content differs, the two vaccines are interchangeable except for a 2-dose series for adolescents age 11 through 15 years, for which only Recombivax HB is approved. Heplisav-B is administered as a 2-dose series on a 0, 1 month schedule and is approved for persons age 18 years or older.

Vaccination Schedule and Use

Infants and Children

HepB vaccination is recommended for all medically stable infants weighing at least 2,000 grams within 24 hours of birth. Only single-component vaccine should be used for the birth dose and doses administered before age 6 weeks. The usual schedule is 0, 1 through 2, and 6 through 18 months.

All pregnant women found to be HBsAg-positive should have their sera tested for HBV DNA. If HBV DNA levels are greater than 200,000 IU/mL, Tenofovir (preferable) or lamivudine should be administered to the pregnant woman starting at the beginning of the third trimester and continued one to three months after birth. Infants born to mothers who are HBsAg-positive should receive the HepB vaccine birth dose and HBIG within 12 hours of birth. HepB vaccine and HBIG should be administered in separate limbs. For infants weighing less than 2,000 grams, the birth dose should not be counted as part of the vaccine series because of potentially reduced immunogenicity; 3 additional doses of vaccine (for a total of 4 doses) should be administered beginning when the infant reaches age 1 month. Infants whose mothers are HBsAg-positive should receive the last dose by age 6 months but not before age 24 weeks.

Infants born to mothers whose HBsAg status is unknown should receive the HepB birth dose within 12 hours of birth. Infants weighing less than 2,000 grams should also receive HBIG within 12 hours of birth. The mother's HBsAg status should be assessed as soon as possible. If the mother is determined to be HBsAg-positive, infants weighing at least 2,000 grams should also receive HBIG as soon as possible but no later than age 7 days. As with infants born to HBsAg-positive mothers, for infants weighing less than 2,000 grams, the birth dose should not be counted as part of the vaccine series because of potentially reduced immunogenicity; 3 additional doses of vaccine (for a total of 4 doses) should be administered beginning when the infant reaches age 1 month. Infants with mothers whose HBsAg status is unknown should receive the last dose by age 6 months but not before age 24 weeks.

Hepatitis B Vaccination Schedule

- Infants: See Hepatitis B vaccine schedule for infants
- Adolescents: All children and adolescents through age 18 years not previously vaccinated
  - 3-dose series at 0, 1, 6 months
  - Adolescents age 11 through 15 years may use 2-dose series of Recombivax HB separated by 4 to 6 months
- Adults: All unvaccinated adults at risk for or requesting protection from HBV infection
  - 2-dose series at 0 and 1 month (Heplisav-B) or 3-dose series at 0, 1 and 6 months (Engerix-B and Recombivax HB)
  - 3-dose series at 0, 1 and 6 months (Twinrix)
  - 3-dose series with doses at 0, 7, 21–30 days, and booster 12 months after dose 1 (Twinrix, accelerated)

Preterm infants weighing less than 2,000 grams have a decreased response to HepB vaccine administered before 1 month of age. However, by chronologic age 1-month preterm infants, regardless of initial birth weight or gestational age, are as likely to respond as adequately as full-term infants. Preterm infants of low birth weight whose mothers are HBsAg-negative can receive the first dose of HepB vaccine at chronologic age 1 month. Preterm infants discharged from the hospital before chronologic age 1 month can receive HepB vaccine at discharge if they are medically stable and have gained weight consistently, even if they are less than 2,000 grams.

The third HepB dose must be administered at least 8 weeks after the second dose, and at least 16 weeks after the first dose. The minimum interval between the first and second dose is 4 weeks.

Hepatitis B vaccine schedules for infants (≥2,000 g birthweight), by maternal HBsAg status

Maternal HBsAg Status	Single-antigen vaccine dose	Single-antigen vaccine age indications	Single-antigen + combination vaccine† dose	Single-antigen + combination vaccine† age indications
Positive	1	Birth (≤12 hrs)	1	Birth (≤12 hrs)
	HBIG§	Birth (≤12 hrs)	HBIG§	Birth (≤12 hrs)
	2	1–2 mos	2	2 mos
	3	6 mos¶	3	4 mos
	N/A	N/A	4	6 mos¶
Unknown*	1	Birth (≤12 hrs)	1	Birth (≤12 hrs)
	2	1–2 mos	2	2 mos
	3	6 mos¶	3	4 mos
	N/A	N/A	4	6 mos¶
Negative	1	Birth (≤24 hrs)	1	Birth (≤24 hrs)
	2	1–2 mos	2	2 mos
	3	6–18 mos¶	3	4 mos
	N/A	N/A	4	6 mos¶

* Mothers should have blood drawn and tested for HBsAg as soon as possible after admission for delivery; if the mother is found to be HBsAg positive, the infant should receive HBIG as soon as possible but no later than age 7 days.

† Pediarix and Vaxelis should not be administered before age 6 weeks.

§ HBIG should be administered at a separate anatomical site from vaccine.

¶ The final dose in the vaccine series should not be administered before age 24 weeks (164 days).

Hepatitis B vaccine schedules for infants (<2,000 g birthweight), by maternal HBsAg status

Maternal HBsAg Status	Single-antigen vaccine dose	Single-antigen vaccine age indications	Single-antigen + combination vaccine† dose	Single-antigen + combination vaccine† age indications
Positive	1	Birth (≤12 hrs)	1	Birth (≤12 hrs)
	HBIG§	Birth (≤12 hrs)	HBIG§	Birth (≤12 hrs)
	2	1 mos	2	2 mos
	3	2–3 mos	3	4 mos
	4	6 mos¶	4	6 mos¶
Unknown	1	Birth (≤12 hrs)	1	Birth (≤12 hrs)
	HBIG§	Birth (≤12 hrs)	HBIG§	Birth (≤12 hrs)
	2	1 mos	2	2 mos
	3	2–3 mos	3	4 mos
	4	6 mos¶	4	6 mos¶
Negative	1	Hospital discharge or age 1 mo	1	Hospital discharge or age 1 mo
	2	2 mos	2	2 mos
	3	6–18 mos¶	3	4 mos
	N/A	N/A	4	6 mos¶

† Pediarix and Vaxelis should not be administered before age 6 weeks.

§ HBIG should be administered at a separate anatomical site from vaccine.

¶ The final dose in the vaccine series should not be administered before age 24 weeks (164 days).

DTaP-HepB-IPV (Pediarix)

DTaP-HepB-IPV vaccine is approved for use as a 3-dose series for children age 6 weeks through 6 years. It is administered to infants at age 2, 4, and 6 months. The minimum intervals for DTaP-HepB-IPV vaccine are determined by the DTaP component. The 3 doses must be separated by at least 4 weeks between doses. Because the minimum age for the first dose of DTaP-HepB-IPV vaccine is 6 weeks, this vaccine cannot be used for the birth dose of HepB vaccine. The final dose of DTaP-HepB-IPV vaccine should be administered at age 24 weeks or older, the minimum age for completion of the HepB vaccine series. When DTaP-HepB-IPV vaccine is used to provide 3 doses at age 2, 4, and 6 months (based on the DTaP and IPV schedules), this will result in a 4-dose HepB vaccine series, which is acceptable.

DTaP-IPV-Hib-HepB (Vaxelis)

DTaP-IPV-Hib-HepB is approved for use as a 3-dose series for children age 6 weeks through 4 years. It is administered to infants at age 2, 4, and 6 months. The minimum intervals for DTaP-IPV-Hib-HepB vaccine are determined by the DTaP component. The 3 doses must be separated by at least 4 weeks between doses. Because the minimum age for the first dose of DTaP-IPV-Hib-HepB vaccine is 6 weeks, this vaccine cannot be used for the birth dose of HepB vaccine. The final dose of DTaP-IPV-Hib-HepB vaccine should be administered at age 24 weeks

or older, the minimum age for completion of the HepB vaccine series. When DTaP-IPV-Hib-HepB vaccine is used to provide 3 doses at age 2, 4, and 6 months (based on the DTaP and IPV schedules), this will result in a 4-dose HepB vaccine series, which is acceptable.

Adolescents

Routine HepB vaccination is recommended for all children and adolescents through age 18 years. All children not previously vaccinated with HepB vaccine should be vaccinated.

An alternative HepB vaccination schedule for adolescents age 11 through 15 years consists of 2 adult doses of Recombivax HB separated by 4 to 6 months. The 2-dose series should be completed by the 16th birthday.

Adults

HepB vaccine is recommended for all unvaccinated adults at risk for HBV infection and for all adults requesting protection from HBV infection. Acknowledgment of a specific risk factor is not a requirement for vaccination.

Adults recommended for HepB vaccination include:

- Persons at risk for infection by sexual exposure, including sex partners of HBsAg-positive persons, persons with more than one sex partner during the previous 6 months, persons seeking evaluation or treatment for a sexually transmitted infection (STI), and MSM
- Household contacts of persons who are HBsAg-positive. They should be screened first for HBsAg, anti-HBc and anti-HBs.
- Persons at risk for infection by percutaneous or mucosal exposure to blood, including current or recent PWID, household contacts of HBsAg-positive persons, residents and staff of facilities for developmentally disabled persons, health care and public safety workers with risk for exposure to blood or blood-contaminated body fluids
- Persons with end-stage renal disease, including predialysis, hemodialysis, peritoneal dialysis, and home dialysis patients
- Persons with diabetes age 19 through 59 years; persons with diabetes age 60 years or older at the discretion of the treating clinician
- Persons with hepatitis C infection or chronic liver disease, including those with cirrhosis, fatty liver disease, alcoholic liver disease, autoimmune hepatitis, and an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level greater than twice the upper limit of normal

- Persons traveling internationally to regions with high or intermediate levels (HBsAg prevalence of 2% or higher) of endemic HBV infection, including those who may engage in high-risk behaviors or provide health care while traveling
- Persons with human immunodeficiency virus (HIV) infection
- Persons who are incarcerated
- All other persons seeking protection from HBV infection

In settings in which a high proportion of adults have risks for HBV infection (e.g., STI/HIV testing and treatment facilities, substance use disorder treatment and prevention settings, health care settings targeting services to PWID or MSM, and correctional facilities), ACIP recommends HepB vaccination for all unvaccinated adults. In other primary care and specialty medical settings in which adults at risk for HBV infection receive care, health care providers should inform all patients about the health benefits of vaccination, risks for HBV infection, and persons for whom vaccination is recommended, and should vaccinate any adults who report risks for HBV infection or request protection from HBV infection.

Heplisav-B

Heplisav-B is approved for use in persons age 18 years or older. The schedule is 2 doses separated by 1 month. Even though Heplisav-B cannot be combined with a different HepB vaccine (e.g., Engerix-B, Recombivax HB, Twinrix) to complete a series, any 2 Heplisav-B doses separated by 4 weeks constitutes a complete HepB vaccine series, even if other doses of Engerix-B, Recombivax HB, or Twinrix, are administered before, after, or between the 2 doses of Heplisav-B, regardless of the interval between these other vaccines and Heplisav-B.

HepA-HepB (Twinrix)

The vaccine is administered in a 3-dose series on a 0, 1, 6 months schedule. Dose 1 and dose 3 should be separated by at least 6 months. Dose 1 and dose 2 should be separated by at least 4 weeks, and dose 2 and dose 3 should be separated by at least 5 months. An alternative Twinrix schedule consists of doses at 0, 7, 21–30 days, and a booster dose at 12 months after the first dose. Because the HepB component of Twinrix is equivalent to a standard adult dose of HepB vaccine, Twinrix can be administered on a single-antigen HepB vaccine schedule; the minimum interval recommendations will be met. Single-antigen HepB vaccine can be used to complete a series begun with Twinrix or vice versa.

Hepatitis B Vaccine Efficacy

- Over 90% of infants, children, adolescents, and healthy adults <40 years develop protective antibody response following complete series
- 80 to 100% effective in preventing infection or clinical hepatitis following complete series
- Larger doses or increased number of doses necessary for dialysis patients and immunocompromised persons
- Booster doses not recommended for immunocompetent persons

Immunogenicity and Vaccine Efficacy

More than 90% of infants, children, and adolescents and more than 90% of healthy adults younger than age 40 years develop a protective antibody response following a complete HepB vaccine series. However, there is an age-specific decline in immunogenicity. By 60 years, only 75% develop protective antibody titers. In adults receiving Heplisav-B, 90 to 100% develop adequate antibody after the 2-dose series.

Infants born to women who are HBsAg-positive are at high risk of HBV transmission and chronic HBV infection. HepB vaccination and 1 dose of HBIG administered within 24 hours after birth are 85% to 95% effective in preventing chronic HBV infection. HepB vaccine administered alone beginning within 24 hours after birth is 70% to 95% effective in preventing perinatal HBV infection.

HepB vaccine is 80% to 100% effective in preventing infection or clinical hepatitis in those who receive the complete vaccine series. Larger vaccine doses (2 to 4 times the normal adult dose) or an increased number of doses are required to induce protective antibody in most dialysis patients age 20 years or older and may also be necessary for other immunocompromised persons age 20 years or older. The recommended dosage of vaccine differs depending on the age of the recipient and type of vaccine.

Available data show that vaccine-induced antibody levels decline with time. However, immune memory remains intact for more than 30 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 those who responded to vaccine.

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

For dialysis patients who did respond to vaccine, the need for booster doses should be assessed by annual testing of vaccine recipients for antibody levels, and a booster dose should be provided when antibody levels decline below 10 mIU/mL.

Seroconversion rates and postvaccination anti-HBs titers are similar among adolescents age 11 through 15 years vaccinated using the 2 adult-dose Recombivax HB schedule compared to those vaccinated using 3 doses.

Serologic Testing of Vaccine Recipients

Prevaccination Serologic Testing

Vaccination of persons immune to HBV because of current or previous infection or HepB vaccination does not increase the risk for adverse events. However, in populations that have high rates of previous HBV infection, prevaccination testing might reduce costs by avoiding vaccination of persons who are already immune. Prevaccination testing consists of testing for HBsAg, anti-HBs, and anti-HBc. Serologic testing should not be a barrier to vaccination of susceptible persons, especially in populations that are difficult to access. Testing is not a requirement for vaccination, and in settings where testing is not feasible, vaccination of recommended persons should continue. The first dose of HepB vaccine should typically be administered immediately after collection of the blood for serologic testing. Prevaccination testing is recommended for household, sexual, or needle-sharing contacts of HBsAg-positive persons; HIV-positive persons; persons with elevated ALT/ AST of unknown etiology; hemodialysis patients; MSM; and past or current PWID.

Serologic testing is not recommended before routine vaccination of infants, children, or adolescents.

Postvaccination Serologic Testing

Testing for immunity following vaccination is not recommended routinely. However, testing is recommended for persons whose subsequent management depends on knowledge of their immune status, including infants born to HBsAg-positive mothers or mothers whose HBsAg status remains unknown (e.g., when a parent or person with lawful custody safely surrenders an infant confidentially shortly after birth), HCP and public safety workers, hemodialysis patients and others who might require outpatient hemodialysis (e.g., predialysis, peritoneal dialysis, and home dialysis), HIV-infected persons, other immunocompromised persons (e.g., hematopoietic stem-cell transplant recipients or persons receiving chemotherapy), and sex partners of HBsAg-positive persons.

Testing should be performed 1 to 2 months after administration of the final dose of the vaccine series using a method that allows determination of a protective concentration of anti-HBs (greater than or equal to 10 mIU/mL). Persons found to have anti-HBs concentrations of greater than or equal to 10 mIU/mL after the primary vaccine series are considered to be immune. Immunocompetent persons have long-term protection and do not need further periodic testing to assess anti-HBs levels. Immunocompromised persons might need annual testing to assess anti-HBs concentrations.

Serologic Testing

Prevaccination

- Consists of testing for HBsAg, anti-HBs, and anti-HBc
- Recommended for:
  - Household, sexual, or needle-sharing contacts of HBsAg-positive persons
  - HIV-positive persons
  - Persons with elevated ALT/ AST of unknown etiology
  - Hemodialysis patients
  - MSM
  - Past or current PWID

Postvaccination

- Not routinely recommended
- Recommended for:
  - Infants born to HBsAg+ women or women with unknown HBsAg status
  - HCP and public safety workers
  - Hemodialysis patients
  - HIV-infected persons
  - Other immunocompromised persons
  - Sex partners of HBsAg+ persons
- Results:
  - Anti-HBs ≥ 10 mIU/mL → Immune
  - Anti-HBs < 10 mIU/mL → Revaccinate

Persons found to have anti-HBs concentrations less than 10 mIU/mL after the primary vaccine series should be revaccinated. Administration of all doses in the second series, on an appropriate schedule, followed by anti-HBs testing 1 to 2 months after the final dose, is usually more practical than serologic testing after one or more doses of vaccine (except for when revaccinating infants born to HBsAg-positive mothers).

Infants born to HBsAg-positive women or HBsAg-unknown women whose status is not determined should be tested for HBsAg and anti-HBs 1 to 2 months after completion of the final dose of the HepB vaccine series, at age 9 through 12 months (generally at the next well-child visit following completion of the HepB vaccine series). If HBsAg is not present and anti-HBs antibody is greater than or equal to 10 mIU/mL, children can be considered to be protected.

HCP who have contact with blood and body fluids of patients who might be infected with HBV, or who are at ongoing risk for injuries with sharp instruments or needlesticks, should be tested for antibody 1 to 2 months after completion of the hepatitis B vaccine series. Increasingly, HCP with documentation of routine HepB vaccination received the series in infancy or as catch-up vaccination in adolescence without postvaccination testing, but they may be tested as a condition of employment. Antibody to vaccine antigen wanes over time, although protection persists in immunocompetent vaccine recipients who responded initially. A negative anti-HBs serologic response in HCP who received HepB vaccine in the distant past will not distinguish between failure to respond to the initial vaccination series (lack of protection) and response to the initial vaccination series with subsequent waning of antibody (protected). Health care institutions may measure anti-HBs upon hire or matriculation for HCP who have documentation of a complete HepB vaccine series in the past (e.g., as part of routine infant or adolescent vaccination). HCP with anti-HBs less than10 mIU/mL should receive one or more additional doses of HepB vaccine and retesting. Institutions that decide to not measure anti-HBs upon hire or matriculation for HCP who have documentation of a complete HepB vaccine series in the past should ensure timely assessment and postexposure prophylaxis following an exposure.

Vaccine Nonresponse

Several factors have been associated with nonresponse to HepB vaccine. These include vaccine factors (e.g., dose, schedule, injection site) and host factors (e.g., older age, male gender). Older age (40 years and older), male gender, obesity, diabetes, smoking, and chronic illness have been independently associated with nonresponse to HepB vaccine. Additional vaccine doses for persons who receive postvaccination testing and who fail to respond to a primary vaccination series administered in the deltoid muscle produce adequate response in 15% to 25% of these persons after 1 additional dose and in 30% to 50% after 3 additional doses.

Persons who do not respond to the first series of HepB vaccine should complete a second vaccine series. The second vaccine series should be given on the usual 0, 1, 6 month schedule. HCP and others for whom postvaccination serologic testing is recommended should be retested 1 to 2 months after completion of the second vaccine series.

Fewer than 5% of persons receiving 6 doses of HepB vaccine administered by the appropriate schedule in the deltoid muscle fail to develop detectable anti-HBs antibody. One reason for persistent nonresponse to HepB vaccine is chronic infection with HBV. Persons who fail to develop detectable anti-HBs after 6 doses should be tested for HBsAg and anti-HBc. Persons who are found to be HBsAg-positive should be counseled accordingly and linked to care with providers experienced in the management of chronic HBV infection. Persons who fail to respond to two appropriately administered series and who are HBsAg-negative should be considered susceptible to HBV infection and should be counseled regarding precautions to prevent HBV infection. They should also be counseled about the need to obtain HBIG prophylaxis for exposure to HBsAg-positive blood.

Vaccine Nonresponse

- Persons who do not respond to the first HepB series should complete a second series on a 0, 1, 6 month schedule
- Retest anti-HBs 1–2 months after completion of second series

Occupational Postexposure Management

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

Postexposure Management of Health Care Personnel after Occupational Exposure to Blood and Body Fluids, by Health Care Personnel HepB Vaccination and Response Status

HepB Vaccination and Response Status	Postexposure testing results for source patient (HBsAg)	Postexposure testing results for HCP (anti-HBs)	HBIG* postexposure prophylaxis	Vaccination postexposure prophylaxis	Postvaccination Serologic Testing†
Documented responder§ after complete series (3 or more doses)	No action needed	No action needed	No action needed	No action needed	No action needed
Documented nonresponder¶ after 2 complete series	Positive/ unknown	**	2 doses HBIG separated by 1 month	No action needed	No action needed
	Negative	No action needed	No action needed	No action needed	No action needed
Response unknown after a complete series	Positive/ unknown	less than 10 mIU/mL**	1 dose HBIG	Initiate revaccination	Yes
	Negative	less than 10 mIU/mL	None	Initiate revaccination	Yes
	Any result	greater than or equal to 10 mIU/mL	No action needed	No action needed	No action needed
Unvaccinated/ incompletely vaccinated or vaccine refusers	Positive/ unknown	**	1 dose HBIG	Complete vaccination	Yes
	Negative	No action needed	None	Complete vaccination	Yes

*HBIG should be administered intramuscularly as soon as possible after exposure when indicated. The effectiveness of HBIG when administered greater than 7 days after percutaneous, mucosal, or nonintact skin exposures is unknown. HBIG and HepB vaccine should be administered in separate anatomic injection sites.

†Should be performed 1 to 2 months after the last dose of the HepB vaccine series (and 4 to 6 months after administration of HBIG to avoid detection of passively administered anti-HBs) using a quantitative method that allows detection of the protective concentration of anti-HBs (greater than or equal to 10 mIU/mL).

§A responder is defined as a person with anti-HBs greater than or equal to 10 mIU/mL after 3 or more doses of HepB vaccine.

¶A nonresponder is defined as a person with anti-HBs less than 10 mIU/mL after 2 complete series of HepB vaccine.

**HCP who have anti-HBs less than 10 mIU/mL, or who are unvaccinated or incompletely vaccinated, and sustain an exposure to a source patient who is HBsAg-positive or has unknown HBsAg status, should undergo baseline testing for HBV infection as soon as possible after exposure and follow-up testing approximately 6 months later. Initial baseline tests consist of total anti-HBc; testing at approximately 6 months consists of HBsAg and total anti-HBc.

Non-Occupational Exposure

Persons who have written documentation of a complete HepB vaccine series and who did not receive postvaccination testing should receive a single vaccine booster dose after non-occupational exposure to an HBsAg-positive source. Persons who are in the process of being vaccinated but who have not completed the vaccine series should complete the

vaccine series and receive the appropriate dose of HBIG as soon as possible. Studies are limited on the maximum interval after exposure during which postexposure prophylaxis is effective, but the interval is unlikely to exceed 7 days for percutaneous exposure and 14 days for sexual exposures. Unvaccinated persons should receive both HBIG and a dose of HepB vaccine as soon as possible after exposure (preferably within 24 hours) and complete the HepB vaccine series according to the appropriate schedule. HepB vaccine may be administered simultaneously with HBIG in a separate injection site, i.e., separate limb.

Hepatitis B Vaccine Contraindications and Precautions

- Contraindication
  - Severe allergic reaction to vaccine component or following a prior dose
  - History of hypersensitivity to yeast
- Precaution
  - Moderate or severe acute illness

Contraindications and Precautions to Vaccination

As with other vaccines, a history of a severe allergic reaction (anaphylaxis) to a vaccine component or following a prior dose is a contraindication to further doses. Moderate or severe acute illness (with or without fever) in a patient is considered a precaution to vaccination, although persons with minor illness may be vaccinated.

In 2011, the Institute of Medicine concluded that the evidence convincingly supports a causal relationship between HepB vaccine and anaphylaxis in yeast-sensitive persons. HepB vaccination is contraindicated for persons with a history of hypersensitivity to yeast or any other vaccine component. The estimated incidence of anaphylaxis among HepB vaccine recipients is 1.1 per million vaccine doses administered.

Some presentations of HepB vaccines contain latex, which may cause allergic reactions.

Vaccination is not contraindicated in persons with a history of multiple sclerosis, Guillain-Barré syndrome, autoimmune disease (e.g., systemic lupus erythematosis or rheumatoid arthritis) or other chronic diseases.

Contraindications to combination vaccines that contain HepB vaccine include the contraindications to the individual component vaccines (e.g., DTaP, hepatitis A); specific ingredients differ by vaccine.

Vaccination during Pregnancy

Pregnancy is not a contraindication to HepB vaccination. Limited data suggest that developing fetuses are not at risk for adverse events when HepB vaccine is administered to pregnant women. Available vaccines contain noninfectious HBsAg and should cause no risk of infection to the fetus.

Pregnant women who are identified as being at risk for HBV infection during pregnancy (e.g., persons with more than one sex partner during the previous 6 months, persons who have

Hepatitis B Vaccine Safety

- Pain
  - 3% to 29%
- Erythema
  - 3%
- Swelling
  - 3%
- Fever
  - 1% to 6%
- Headache
  - 3%

been evaluated or treated for an STI, recent or current PWID, or persons who have had an HBsAg-positive sex partner) should be vaccinated.

Heplisav-B is not recommended in pregnancy, based on a lack of available safety data.

Vaccine Safety

In prelicensure trials, adverse events following HepB vaccination were most commonly injection site reactions and mild systemic reactions. Commonly reported mild adverse events from postmarketing data include pain (3% to 29%), erythema (3%), swelling (3%), fever (1% to 6%), and headache (3%).

In rare instances, other illnesses have been reported after HepB vaccination, including Guillain-Barré syndrome, chronic fatigue syndrome, neurologic disorders (e.g., leukoencephalitis, optic neuritis, and transverse myelitis), rheumatoid arthritis, type 1 diabetes, and autoimmune disease. However, no causal association between those conditions or any other chronic illness and HepB vaccine has been demonstrated. Reviews by scientific panels have also found no causal association between HepB vaccination and multiple sclerosis.

Reported episodes of alopecia (hair loss) after rechallenge with HepB vaccine suggest that vaccination might very rarely trigger alopecia. "Rechallenge" in this context means the same adverse event occurs twice, each time after sequential doses of vaccine. Some cases were transient. However, a population-based study found no statistically significant association between alopecia and Hep B vaccination.

Vaccine Storage and Handling

HepB vaccine should be maintained at refrigerator temperature between 2°C and 8°C (36°F and 46°F). Manufacturer package inserts contain additional information. For complete information on best practices and recommendations, please refer to CDC's Vaccine Storage and Handling Toolkit, www.cdc.gov/vaccines/hcp/admin/storage/toolkit/storage-handling-toolkit.pdf.

Surveillance and Reporting of Hepatitis B

Hepatitis B infection is nationally notifiable in the United States. For information on guidance for state and local health department staff who are involved in surveillance activities for vaccine-preventable diseases, please consult the Manual for the Surveillance of Vaccine-Preventable Diseases, www.cdc.gov/vaccines/pubs/surv-manual/chapters.html.

Acknowledgements

The editors would like to acknowledge Maria Cano and Phil Spradling for their contributions to this chapter.

Selected References

Ascherio A, Zhang S, Hernán M, et al. Hepatitis B vaccination and the risk of multiple sclerosis. *N Engl J Med* 2001;344(5):327–32.

CDC. CDC guidance for evaluating health-care personnel for hepatitis B virus protection and for administering posexposure management. *MMWR* 2013;62(RR-10):1–19.

CDC. CDC Yellow Book 2018: Health Information for International Travel. New York: Oxford University Press;2017.

CDC. Immunization of health-care personnel. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2011;60(RR-7):1–45.

CDC. Prevention of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. *MMWR* 2018;67(1):1–31.

CDC. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. *MMWR* 2008;57(RR-8):1–20.

CDC. Use of hepatitis B vaccination for adults with diabetes mellitus. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2011;60(50):1709–11 .

Institute of Medicine. *Adverse effects of vaccines: Evidence and causality*. Washington D.C.: The National Academies Press;2011.

Institute of Medicine. *Immunization Safety Review: Hepatitis B Vaccine and Demyelinating Neurological Disorders*. Washington D.C.: The National Academy Press;2002.

Lewis E, Shinefield H, Woodruff B, et al. Safety of neonatal hepatitis B vaccine administration. *Pediatr Infect Dis J* 2001;20(11):1049–54.

Poland G, Jacobson R. Clinical practice: prevention of hepatitis B with the hepatitis B vaccine. *N Engl J Med* 2004;351(27):2832–8.

Van Damme P, Ward J, Shouval D, et al. Hepatitis B Vaccines. In: Plotkin S, Orenstein W, Offit P, et al., eds. Plotkin's *Vaccines*. 7th ed. Elsevier;2018:342–74.

NOTES

NOTES

Human Papillomavirus

Elissa Meites, MD, MPH; Julianne Gee, MPH; Elizabeth Unger, PhD, MD; and Lauri Markowitz, MD

Human papillomavirus (HPV) is the most common sexually transmitted infection in the United States. Although the majority of HPV infections are asymptomatic and resolve spontaneously, persistent infections can develop into anogenital warts, precancers, and cervical, anogenital, or oropharyngeal cancers in women and men. The relationship between cervical cancer and sexual behavior was suspected for more than 100 years and was established by epidemiologic studies in the 1960s. In the early 1980s, cervical cancer cells were shown to contain HPV DNA. Epidemiologic studies demonstrating a consistent association between HPV and cervical cancer were published in the 1990s; more recently, HPV has been identified as a cause of certain other mucosal cancers. A quadrivalent vaccine to prevent infection with four types of HPV was licensed for use in the United States in 2006, a bivalent vaccine was licensed in 2009, and a 9-valent vaccine was licensed in 2014.

Human Papillomaviruses

HPV consists of a family of small, double-stranded DNA viruses that infect the epithelium. More than 200 distinct types have been identified; they are differentiated by their genomic sequence. Most HPV types infect the cutaneous epithelium and can cause common skin warts. About 40 types infect the mucosal epithelium; these are categorized according to their epidemiologic association with cervical cancer.

Infection with low-risk or nononcogenic types, such as types 6 or 11, can cause benign or low-grade cervical cell abnormalities, anogenital warts, and respiratory tract papillomas. More than 90% of cases of anogenital warts are caused by low-risk HPV types 6 or 11.

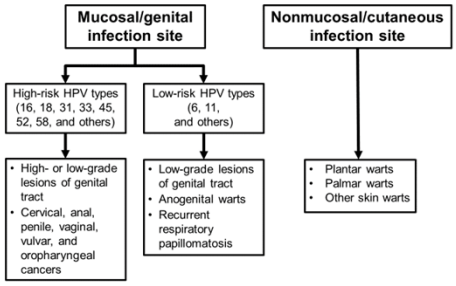
High-risk or oncogenic HPV types act as carcinogens in the development of cervical cancer and other anogenital cancers. High-risk types (including types 16, 18, and others) can cause low-grade cervical cell abnormalities, high-grade cervical cell abnormalities that are precursors to cancer, and anogenital cancers. High-risk HPV types are detected in 99% of cervical precancers. Type 16 is the cause of approximately 50% of cervical cancers worldwide, and types 16 and 18 together account for about 66% of cervical cancers. An additional five high-risk types, 31, 33, 45, 52, and 58, are responsible for another 15% of cervical cancers and 11% of all HPV-associated cancers. Infection with a high-risk HPV type is considered necessary for the development of cervical cancer but, by itself, is not sufficient to cause cancer. The vast majority of women with HPV infection, even those with high-risk HPV types, do not develop cancer.

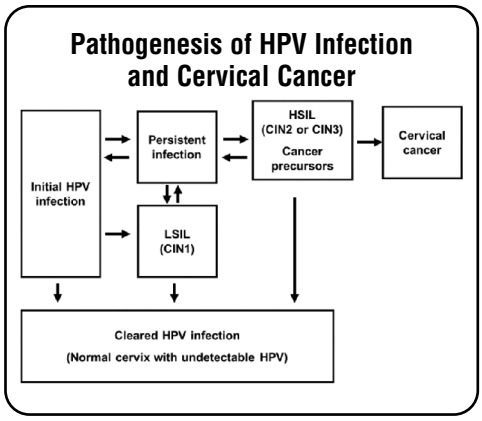
In addition to cervical cancer, high-risk HPV infection is associated with less common anogenital cancers, such as cancer of the vulva, vagina, penis, and anus. These HPV types can also cause oropharyngeal cancers.

Human Papillomaviruses (HPV)

- Small DNA virus
- More than 200 types have been identified
- Most HPV types infect the cutaneous epithelium and can cause common skin warts
- About 40 types infect the mucosal epithelium

Human Papillomavirus Types and Disease Association





Pathogenesis

HPV infection occurs at the basal epithelium. Although incidence of infection is high, most infections resolve spontaneously within a year or two. A small proportion of infected persons become persistently infected; persistent infection is the most important risk factor for the development of cervical cancer.

In women, squamous intraepithelial lesions (SIL) of the cervix can be detected through screening. Low-grade squamous intraepithelial lesions (LSIL) often regress. High-grade squamous intraepithelial lesions (HSIL) are considered cancer precursors. Previously, these types of cervical lesions were called cervical intraepithelial neoplasia (CIN). If left undetected and untreated, such cancer precursors can progress to cervical cancer years or decades later.

The pathogenesis of other types of HPV-related cancers may follow a similar course, although less is known about their respective precursor lesions: anal HSIL has been identified as a precursor to anal cancer, vulvar HSIL has been identified as a precursor to vulvar cancer, and vaginal HSIL has been identified as a precursor to vaginal cancer.

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

HPV Clinical Features

- Most HPV infections are asymptomatic and result in no clinical disease
- Clinical manifestations of HPV infection include:
  - Anogenital warts
  - Recurrent respiratory papillomatosis
  - Cervical cancer precursors (HSIL)
  - Cancer (cervical, anal, vaginal, vulvar, penile, and oropharyngeal cancer)

Clinical Features

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

Laboratory Testing

HPV is not cultured by conventional methods. Infection is identified by detection of HPV DNA from clinical specimens. Assays for HPV detection differ considerably in their sensitivity and type specificity, and detection is also affected by the anatomic region sampled, as well as the method of specimen collection.

Several HPV tests have been approved by the Food and Drug Administration (FDA) and detect up to 14 high-risk types (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68). Test results are reported as positive when the presence of any combination of these HPV types is detected; certain tests specifically identify HPV types 16 and/or 18. These tests are approved for use in women as part of cervical cancer screening either as primary

screen, co-test with cytology, or management of abnormal cervical cytology results on a Papanicolaou (Pap) test. HPV tests are neither clinically indicated nor approved for use in men.

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

The most frequently used HPV serologic assays are virus-like-particle-(VLP)-based enzyme immunoassays. However, laboratory reagents used for these assays are not standardized and there are no standards for setting a threshold for a positive result. Serology results are not used clinically.

Medical Management

No specific treatment is required or recommended for asymptomatic HPV infection. Medical management is recommended for treatment of specific clinical manifestations of HPV-related disease (e.g., anogenital warts, precancerous lesions, or cancers).

Epidemiology

Occurrence

HPV infection is extremely common throughout the world. Most sexually active adults will have an HPV infection at some point during their lives, although they may be unaware of their infection.

Reservoir

Humans are the only natural reservoir for HPV. Other viruses in the papillomavirus family affect other species.

Transmission

HPV is transmitted through intimate, skin-to-skin contact with an infected person. Transmission is most common during vaginal, penile, anal, or oral sex.

Studies of newly acquired HPV infection demonstrate that infection typically occurs soon after first sexual activity. In a prospective study of college women, the cumulative incidence of infection was 40% by 24 months after first sexual intercourse, and 10% of infections were caused by HPV 16.

Autoinoculation from one body site to another can occur.

Very rarely, vertical transmission of HPV from an infected mother to her infant can result in a condition called juvenile-onset recurrent respiratory papillomatosis.

HPV Epidemiology

- Reservoir
  - Human
- Transmission
  - Direct contact, usually sexual
- Temporal pattern
  - None
- Communicability
  - Presumed to be high
- Risk factors
  - Sexual behavior, including higher number of lifetime and recent sex partners

Temporal Pattern

There is no known seasonal variation in HPV infection.

Communicability

HPV is presumed to be communicable during both acute and persistent infections. Communicability can be presumed high because of the large number of new infections estimated to occur each year.

Risk Factors

Risk factors for HPV infection are primarily related to sexual behavior, including higher numbers of lifetime and recent sex partners. Results of epidemiologic studies are less consistent for other risk factors, including younger age at sexual initiation, higher number of pregnancies, genetic factors, smoking, and lack of circumcision of the male partner.

HPV Secular Trends in the United States

- Genital HPV is the most common sexually transmitted infection in the U.S.
- Common among adolescents and young adults
- Before vaccine introduction
  - Estimated 79 million infected
  - 14 million new infections/year
- Within 10 years following vaccine introduction, prevalence of HPV types 6, 11, 16, and 18 has decreased:
  - 86% among females age 14 through 19 years
  - 71% among females age 20 through 24 years

Secular Trends in the United States

Genital HPV infection is the most common sexually transmitted infection in the United States and worldwide.

Based on data from 2003-2006 (before vaccine introduction), an estimated 79 million persons were infected in the United States. Approximately 14 million new HPV infections occurred annually, with nearly half occurring in persons age 15 through 24 years. During 2013–2014, genital prevalence of any of 37 HPV types assayed was 45.2% and prevalence of high-risk HPV types was 25.1% among U.S. men age 18 through 59 years. Also during this period, genital prevalence of any of 37 HPV types assayed was 39.9% and prevalence of high-risk HPV types was 20.4% among U.S. women in the same age range. Within a decade following the U.S. introduction of quadrivalent HPV vaccine in 2006, prevalence of HPV types 6, 11, 16, and 18 decreased 86% among females age 14 through 19 years and decreased 71% among females age 20 through 24 years.

The National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER) program and CDC's National Program of Cancer Registries provide data on the number of HPV cancers in the United States. On average, 43,999 HPV-associated cancers are reported annually, including 24,886 in females and 19,113 in males. By gender, the most common cancers attributed to HPV are an estimated 10,900 cervical cancers in women and 11,300 oropharyngeal cancers in men.

In addition to 91% of cervical cancer, HPV is responsible for about 91% of anal cancers, 69% of vulvar cancers, 75% of vaginal cancers, 63% of penile cancers, and 70% of oropharyngeal cancers.

On the basis of health claims data in the United States, the incidence of anogenital warts in 2004 (before vaccine introduction) was 1.2 per 1,000 females and 1.1 per 1,000 males. During 2003–2010, reductions in anogenital wart prevalence were observed among U.S. females age 15 through 24 years, the group most likely to be affected by introduction of HPV vaccine. By 2014, decreasing prevalence of anogenital warts was also identified in young men.

From 2008–2015, both CIN grade 2 or worse (CIN2+) rates and cervical cancer screening declined among women age 18 through 24 years. Significant decreases in CIN2+ rates among screened women in this age group were consistent with population-level impact of HPV vaccination.

Among adolescents age 13 through 17 years in 2019, 71.5% had received at least 1 dose of HPV vaccine, and 54.2% were up-to-date with HPV vaccination (including adolescents who received an HPV vaccine series of 2 doses initiated before age 15 years, or else 3 doses, at the recommended intervals). Among females, 73.2% had received at least 1 dose of HPV vaccine and 56.8% were up-to-date with HPV vaccination. Among males, 69.8% had received at least 1 dose of HPV vaccine and 51.8% were up-to-date with HPV vaccination. Each of these coverage estimates represents a statistically significant increase in HPV vaccination coverage from 2018.

Prevention

Vaccination prevents HPV infection, benefitting both the vaccinated person and their future sex partners by preventing spread of HPV. HPV transmission can be reduced, but not eliminated, with the consistent and correct use of physical barriers such as condoms.

Cervical Cancer Screening

Most cases of and deaths from cervical cancer can be prevented through screening and treatment. The Pap test detects precancerous changes in cervical cells collected by a health care provider and placed on a slide (a conventional Pap) or in liquid media (liquid-based cytology). Clinical tests for HPV can be used as a primary screen either alone or in combination with cytology (co-test) or as triage after an equivocal cytology result.

Recommendations for cervical cancer screening in the United States are based on systematic evidence reviews by major medical and other organizations including the U.S. Preventive Services Task Force (USPSTF), American Cancer Society (ACS), and the American College of Obstetricians and Gynecologists (ACOG). Annual cervical cancer screening is not recommended for average-risk individuals. Instead, cytology testing is

Cervical Cancer Screening

- Annual cervical cancer screening not recommended for average-risk individuals
- For ages 21 through 29 years, screen with cytology testing every 3 years
- For ages 30 through 65 years, screen with choice of cytology test every 3 years, an HPV test alone every 5 years, or cytology test plus HPV test every 5 years
- USPSTF and ACOG have similar screening recommendations; ACS recommends that screening start at age 25 years for average-risk persons
- HPV vaccination does not eliminate the need for cervical cancer screening

recommended every 3 years from age 21 through 29 years. Between age 30 and 65 years, a choice of a cytology test every 3 years, an HPV test alone every 5 years, or cytology test plus an HPV test (co-test) every 5 years is recommended. Co-testing can be done by either collecting one sample for the cytology test and another for the HPV test or by using the remaining liquid cytology material for the HPV test. Cervical screening programs should screen those who have received HPV vaccination in the same manner as those who are unvaccinated. Screening is not recommended before age 21 years in those at average risk. For those age 30 to 65 years, cytology alone or primary HPV testing are preferred by USPSTF, but co-testing can be used as an alternative approach. USPSTF and ACOG have similar screening recommendations. ACS recommends that screening start at age 25 years for average-risk persons.

HPV vaccination does not eliminate the need for continued cervical cancer screening, since up to 30% of cervical cancers are caused by HPV types not prevented by the quadrivalent or bivalent vaccines, and 15% of cervical cancers are caused by HPV types not prevented by the 9-valent vaccine.

HPV Vaccines

- 9vHPV (Gardasil 9) is licensed and currently distributed in the U.S.
  - Prevents HPV types 6, 11, 16, 18, 31, 33, 45, 52, 58
- 4vHPV and 2vHPV are licensed but not currently distributed in the U.S.
  - 4vHPV prevents HPV types 6, 11, 16, 18
  - 2vHPV prevents HPV types 16, 18

HPV Vaccine Characteristics

- HPV L1 major capsid protein of the virus is antigen used for immunization
- L1 protein produced using recombinant technology
- L1 proteins self-assemble into virus-like particles (VLP)
- VLPs are noninfectious and nononcogenic
- Administer by intramuscular injection
- 9vHPV contains yeast protein
- 9vHPV contains aluminum adjuvant

Human Papillomavirus Vaccines

A 9-valent recombinant protein subunit HPV vaccine (9vHPV, Gardasil 9) is licensed for use and is currently distributed in the United States. Two additional HPV vaccines remain licensed in the United States but are not currently distributed: a quadrivalent HPV vaccine (4vHPV, Gardasil), and a bivalent HPV vaccine (2vHPV, Cervarix). All of the vaccines prevent infection with high-risk HPV types 16 and 18, types that cause most cervical and other cancers attributable to HPV; 9vHPV vaccine also prevents infection with five additional high-risk types. In addition, 4vHPV and 9vHPV vaccines prevent infections with HPV types 6 and 11, types that cause anogenital warts.

Characteristics

The antigen for HPV vaccines is the L1 major capsid protein of HPV, produced by using recombinant DNA technology. L1 proteins self-assemble into noninfectious, nononcogenic units called virus-like particles (VLPs). The L1 proteins are produced by fermentation using *Saccharomyces cerevisiae* yeast; 9vHPV vaccine contains yeast protein. 9vHPV vaccine contains VLPs for nine HPV types: two types that cause anogenital warts (HPV types 6 and 11) and seven types that can cause cancers (HPV types 16, 18, 31, 33, 45, 52, and 58). 9vHPV vaccine is administered by intramuscular injection. Each dose of 9vHPV vaccine contains aluminum as an adjuvant. It contains no antibiotic or preservative.

Vaccination Schedule and Use

HPV vaccination is recommended for females and males at age 11 or 12 years for prevention of HPV infections and HPV-associated diseases, including certain cancers. The vaccination series can be started at age 9 years. Catch-up HPV vaccination is recommended for all persons through age 26 years who are not adequately vaccinated. Catch-up HPV vaccination is not recommended for all adults older than age 26 years, since the public health benefit of vaccination in this age range is minimal. HPV vaccines are not licensed for use in persons older than age 45 years.

HPV vaccines are administered as a 2- or 3-dose series, depending on age at initiation and medical conditions.

A 2-dose series is recommended for persons who receive the first valid dose before their 15th birthday (except for persons with certain immunocompromising conditions). The second and final dose should be administered 6 through 12 months after the first dose (0, 6–12 month schedule). If dose 2 is administered at least 5 months after the first dose, it can be counted as valid. If dose 2 is administered at a shorter interval, an additional dose should be administered at least 12 weeks after dose 2 and at least 6 to 12 months after dose 1.

A 3-dose series is recommended for persons who receive the first valid dose on or after their 15th birthday, and for persons with primary or secondary immunocompromising conditions that might reduce cell-mediated or humoral immunity, such as B lymphocyte antibody deficiencies, T lymphocyte complete or partial defects, human immunodeficiency virus (HIV) infection, malignant neoplasm, transplantation, autoimmune disease, or immunosuppressive therapy, in whom immune response to vaccination may be attenuated. In a 3-dose schedule, dose 2 should be administered 1–2 months after dose 1, and dose 3 should be administered 6 months after dose 1 (0, 1–2, 6 month schedule).

There is no maximum interval between doses. If the HPV vaccination schedule is interrupted, the vaccine series does not need to be restarted. For persons who already received 1 dose of HPV vaccine before their 15th birthday, and now are age 15 years or older, the 2-dose series is considered adequate. If the series was interrupted after dose 1, dose 2 should be administered as soon as possible.

Routine HPV vaccination is recommended beginning at 9 years of age for children with any history of sexual abuse or assault.

Ideally, vaccine should be administered before any exposure to HPV through sexual contact. However, persons in the

HPV Vaccination Schedule

- Routine vaccination recommended for females and males at age 11 or 12 years (minimum age 9 years)
- Catch-up vaccination recommended for all persons not adequately vaccinated through age 26 years
- Catch-up vaccination not recommended for all adults over age 26 years
- Shared clinical decision-making is recommended for some adults age 27 through 45 years
- Not licensed for adults over age 45

HPV Vaccination Schedule

- 2-dose series
  - For immunocompetent persons who receive first valid dose before 15th birthday
  - 0, 6–12 month schedule
  - Minimum interval of 5 months
- 3-dose series
  - For persons who receive first valid dose on or after 15th birthday
  - For persons with primary or secondary immunocompromising conditions
  - 0, 1–2, 6 month schedule
- Series does not need to be restarted if the schedule is interrupted
- Prevaccination assessments not recommended
- No therapeutic effect on existing HPV infection, anogenital warts, or HPV-related lesions

routine and catch-up age ranges (through age 26 years) should be vaccinated, even if they might have been exposed to HPV in the past.

Vaccination will provide less benefit to sexually active persons who have been already infected with one or more HPV vaccine types. However, HPV vaccination can provide protection against HPV vaccine types not already acquired. Recipients may be advised that prophylactic vaccine is not expected to have a therapeutic effect on existing HPV infection, anogenital warts, or HPV-related lesions.

HPV vaccine should be administered at the same visit as other age-appropriate vaccines, such as Tdap and quadrivalent meningococcal conjugate (MenACWY) vaccines. Administering all indicated vaccines at a single visit increases the likelihood that patients will receive each of the vaccines on schedule. Each vaccine should be administered using a separate syringe at a different anatomic site.

Catch-up vaccination is recommended through age 26 years. Above this age, shared clinical decision-making regarding HPV vaccination is recommended for some adults age 27 through 45 years who are not adequately vaccinated. HPV vaccination does not need to be discussed with most adults over age 26 years; clinicians can consider discussing HPV vaccination with persons who are most likely to benefit.

Considerations for shared clinical decision-making regarding HPV vaccination of adults age 27 through 45 years include:

- HPV is a very common sexually transmitted infection. Most HPV infections are transient and asymptomatic and cause no clinical problems.
- Although new HPV infections are most commonly acquired in adolescence and young adulthood, some adults are at risk for acquiring new HPV infections. At any age, having a new sex partner is a risk factor for acquiring a new HPV infection.
- Persons who are in a long-term, mutually monogamous sexual partnership are not likely to acquire a new HPV infection.
- Most sexually active adults have been exposed to some HPV types, although not necessarily to all of the HPV types targeted by vaccination.
- No clinical antibody test can determine whether a person is already immune or still susceptible to any given HPV type.
- HPV vaccine efficacy is high among persons who have not been exposed to vaccine-type HPV before vaccination.

- Vaccine effectiveness might be low among persons with risk factors for HPV infection or disease (e.g., adults with multiple lifetime sex partners and likely previous infection with vaccine-type HPV), as well as among persons with certain immunocompromising conditions.
- HPV vaccines are prophylactic (i.e., they prevent new HPV infections). They do not prevent progression of HPV infection to disease, decrease time to clearance of HPV infection, or treat HPV-related disease.

Prevaccination assessments (e.g., HPV testing of any kind, cervical cancer screening or Pap testing, pregnancy testing, or "virginity testing") are not required. No prevaccination testing (e.g., Pap or HPV testing) is recommended to establish the appropriateness of HPV vaccination.

The Advisory Committee on Immunization Practices (ACIP) has not preferentially recommended any of the licensed HPV vaccines. There is no ACIP recommendation for additional vaccination with 9vHPV for persons who have completed a series with one of the other recommended HPV vaccines.

Vaccine recipients should always be seated during vaccine administration. Because syncope has sometimes been reported in association with HPV vaccination, clinicians should consider observing recipients for 15 minutes after vaccination.

Immunogenicity and Vaccine Efficacy

HPV vaccine is highly immunogenic. More than 98% of recipients develop an antibody response to each covered HPV type within one month after completing the vaccine series. However, there is no known serologic correlate of protection and the minimum antibody titer needed for protection has not been determined. The high efficacy found in the clinical trials has precluded identification of this threshold. Further follow-up of vaccinated cohorts might allow determination of serologic correlates of protection in the future.

All licensed HPV vaccines have high efficacy for prevention of HPV vaccine-type-related persistent infection, CIN2+, and adenocarcinoma in-situ (AIS). Prelicensure, clinical efficacy for 4vHPV was assessed in phase III clinical trials. To date, ongoing monitoring has demonstrated that vaccine effectiveness remains above 90%, with no waning of immunity through at least 10 to 12 years after immunization.

Although high efficacy was demonstrated among persons without evidence of prior infection with HPV vaccine types in clinical trials, there was no evidence of efficacy against disease caused by vaccine types with which participants were already infected at the time of vaccination (i.e., the vaccines had no therapeutic effect on existing infection or disease).

HPV Vaccine Efficacy

- High vaccine efficacy
- More than 98% of recipients develop an antibody response to covered HPV types within one month after completing the series
- No evidence of efficacy against disease caused by vaccine types with which participants were infected at the time of vaccination
- Prior infection with one HPV type did not diminish efficacy of the vaccine against other vaccine HPV types

Participants infected with one or more HPV vaccine types prior to vaccination were protected against disease caused by the other vaccine types. Prior infection with one HPV type did not diminish vaccine efficacy against other HPV vaccine types.

Contraindications and Precautions to Vaccination

As with other vaccines, a history of a severe allergic reaction (anaphylaxis) to a vaccine component or following a prior dose is a contraindication to further doses. Moderate or severe acute illness (with or without fever) in a patient is considered a precaution to vaccination, although persons with minor illness may be vaccinated.

Both 4vHPV and 9vHPV are produced using Saccharomyces cerevisiae (baker's yeast) and thus are contraindicated for persons with a history of immediate hypersensitivity to yeast. 2vHPV should not be used in persons with an anaphylactic allergy to latex as the pre-filled syringes might contain latex in the tip cap.

Vaccination during Pregnancy

HPV vaccines are not recommended for use during pregnancy. If a person is found to be pregnant after starting the vaccine series, the remainder of the series should be delayed until after pregnancy. If a vaccine dose has been administered during pregnancy, no intervention is needed. Pregnancy testing is not needed before vaccination.

A pregnancy registry has been established by the manufacturer of 9vHPV. Women exposed to this vaccine around the time of conception or during pregnancy are encouraged to be registered by calling 1-800-986-8999 (merckpregnancyregistries.com/gardasil9.html).

Persons who are lactating or breastfeeding can receive HPV vaccine.

Vaccine Safety

HPV vaccine is generally well-tolerated. Safety has been well-established from prelicensure trials and postlicensure monitoring and evaluation.

The most common adverse reactions reported during clinical trials of HPV vaccines were local reactions at the site of injection. In prelicensure clinical trials, local reactions, such as pain, redness, or swelling were reported by 20% to 90% of recipients. A temperature of 100°F during the 15 days after

HPV Vaccine Contraindications and Precautions

- Contraindication
  - Severe allergic reaction to a vaccine component or following a prior dose
  - History of immediate hypersensitivity to yeast (4vHPV and 9vHPV only)
  - Anaphylactic allergy to latex (2vHPV only)
- Precaution
  - Moderate or severe acute illnesses (defer until symptoms improve)

HPV Vaccination During Pregnancy

- Initiation of the vaccine series should be delayed until after completion of pregnancy
- If a woman is found to be pregnant after initiating the vaccination series, remaining dose(s) should be delayed until after the pregnancy
- If a vaccine dose has been administered during pregnancy, there is no indication for intervention
- Women vaccinated during pregnancy should be reported to the manufacturer
- Pregnancy testing is not needed before vaccination

vaccination was reported by 10% to 13% of HPV vaccine recipients. A similar proportion of placebo recipients reported an elevated temperature. Local reactions generally increased in frequency with increasing doses. However, reports of fever did not increase significantly with increasing doses. Although rare, anaphylaxis can occur. No other serious adverse events have been significantly associated with any HPV vaccine, based on monitoring by CDC and FDA.

A variety of systemic adverse events following vaccination were reported by vaccine recipients, including nausea, dizziness, myalgia, and malaise. However, these symptoms occurred with similar frequency among vaccine and placebo recipients.

Postlicensure monitoring of reports from the Vaccine Adverse Event Reporting System (VAERS) did not identify any unexpected adverse event, was consistent with data from prelicensure clinical trials, and supports the safety data for 9vHPV. The Vaccine Safety Datalink did not identify any new safety concerns after monitoring around 839,000 doses of 9vHPV administered during 2015–2017.

Because syncope has sometimes been reported, vaccine recipients should always be seated during vaccine administration. Clinicians should consider observing recipients for 15 minutes after vaccination.

HPV Vaccine Safety

- HPV vaccine is generally well-tolerated
- Local reactions (pain, redness, swelling)
  - 20%-90%
- Fever (100%)
  - 10%-13% (similar to reports in placebo recipients)
- Anaphylaxis is rare, but can occur
- No other serious adverse reactions associated with any HPV vaccine

Vaccine Storage and Handling

HPV vaccines should be maintained at refrigerator temperature between 2°C and 8°C (36°F and 46°F). Manufacturer package inserts contain additional information. For complete information on best practices and recommendations for vaccine storage and handling, please refer to CDC's Vaccine Storage and Handling Toolkit, www.cdc.gov/vaccines/hcp/admin/storage/toolkit/storage-handling-toolkit.pdf.

Surveillance and Reporting of HPV Infection

HPV infection is not a nationally notifiable condition. For information on guidance for state and local health department staff who are involved in surveillance activities for vaccine-preventable diseases, please consult the Manual for the Surveillance of Vaccine-Preventable Diseases, www.cdc.gov/vaccines/pubs/surv-manual/chapters.html.

Acknowledgements

The editors would like to acknowledge Valerie Morelli, Ginger Redmon, and Mona Saraiya for their contributions to this chapter.

NOTES

Selected References

CDC. Human papillomavirus vaccination for adults: updated recommendations of the Advisory Committee on Immunization Practices. *MMWR* 2019;68(32):698–702.

CDC. Human papillomavirus vaccination: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2014;63(RR-05):1–30.

CDC. Use of a 2-dose schedule for human papillomavirus vaccination—updated recommendations of the Advisory Committee on Immunization Practices. *MMWR* 2016;65(49):1405–8.

CDC. Use of 9-valent human papillomavirus (HPV) vaccine: updated HPV vaccination recommendations of the Advisory Committee on Immunization Practices. *MMWR* 2015;64(11):300–4.

Curry S, Krist A, Owens D, et al.; US Preventive Services Task Force. Screening for cervical cancer: US Prevention Services Task Force recommendation statement. *JAMA* 2018;320(7):674–86.

Donahue J, Kieke B, Lewis E, et al. Near real-time surveillance to assess the safety of the 9-valent human papillomavirus vaccine. *Pediatrics* 2019 Dec:144(6):e20191808.

Drolet M, Bénard É, Pérez N, et al; Vaccination Impact Study Group. Population-level impact and herd effects following the introduction of human papillomavirus vaccination programmes: updated systematic review and meta-analysis. *Lancet* 2019;394(10197):497–509.

Fontham E, Wolf A, Church T, et al. Cervical cancer screening for individuals at risk: 2020 guidelines update from the American Cancer Society. *Cancer J Clin* 2020;1–26.

Food and Drug Administration. Prescribing information (package insert). Gardasil 9 (human papillomavirus 9-valent vaccine, recombinant). Silver Spring, MD: U.S. Department of Health and Human Services, Food and Drug Administration; 2020. https://www.fda.gov/media/90064/download. Accessed September 10, 2020.

FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N Engl J Med* 2007;356(19):1915–27.

Gargano J, Park I, Griffin M, et al. Trends in high-grade cervical lesions and cervical cancer screening in 5 states, 2008–2015. *Clin Infect Dis* 2019;68(8):1282–91.

Garland S, Hernandez-Avila M, Wheeler C, et al; Females United to Unilaterally Reduce Endo/Ectocervical Disease (FUTURE) I Investigators. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. *N Engl J Med* 2007;356(19):1928–43.

Giuliano A, Palefsky J, Goldstone S, et al. Efficacy of quadrivalent HPV vaccine against HPV infection and disease in males. *N Engl J Med* 2011;364(5):401–11.

Iverson O, Miranda M, Ulied A, et al. Immunogenicity of the 9-valent HPV vaccine using 2-dose regimens in girls and boys vs a 3-dose regimen in women. *JAMA* 2016;316(22):2411–21.

Joura E, Giuliano A, Iversen O, et al. Broad Spectrum HPV Vaccine Study. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. *N Engl J Med* 2015;372(8):711–23.

Kjaer S, Nygård M, Dillner J, et al. A 12-year follow-up on the long-term effectiveness of the quadrivalent human papillomavirus vaccine in 4 Nordic countries. *Clin Infect Dis* 2018;66(3):339–45.

McClung N, Lewis R, Gargano J, et al. Declines in vaccine-type human papillomavirus prevalence in females across racial/ethnic groups: data from a national survey. *J Adolesc Health* 2019;65(6):715–22.

Moreira E Jr., Block S, Ferris D, et al. Safety profile of the 9-valent HPV vaccine: a combined analysis of 7 phase III clinical trials. *Pediatrics* 2016;138(2):e20154387.

Muñoz N, Bosch F, de Sanjosé S, et al; International Agency for Research on Cancer Multicenter Cervical Cancer Study Group. Epidemiologic classification of human papillomavirus types associated with cervical cancer. *N Engl J Med* 2003;348(6):518–27.

Owusu-Edusei K Jr., Chesson H, Gift T, et al. The estimated direct medical cost of selected sexually transmitted infections in the United States, 2008. *Sex Transm Dis* 2013;40(3):197–201.

Palefsky J, Giuliano A, Goldstone S, et al. HPV vaccine against anal HPV infection and anal intraepithelial neoplasia. *N Engl J Med* 2011;365(17):1576–85.

Phillips A, Patel C, Pillsbury A, et al. Safety of human papillomavirus vaccines: an updated review. *Drug Saf* 2018;41(4):329–46.

NOTES

NOTES

Satterwhite C, Torrone E, Meites E, et al. Sexually transmitted infections among US women and men: prevalence and incidence estimates, 2008. *Sex Transm Dis* 2013;40(3):187–93.

Senkomago V, Henley S, Thomas C, et al. Human papillomavirus-attributable cancers—United States, 2012–2016. *MMWR* 2019;68(33):724–8.

Shimabukuro T, Su J, Marques P, et al. Safety of the 9-valent human papillomavirus vaccine. *Pediatrics*. 2019;144(6):e20191791.

Winer R, Lee S, Hughes J, et al. Genital human papillomavirus infection incidence and risk factors in a cohort of female university students. *Am J Epidemiol* 2003;157(3):218–26.

Elisha Hall, PhD, RD

Influenza is an infectious viral illness. The name "influenza" originated in 15th century Italy, from an epidemic attributed to "influence of the stars." The first documented pandemic, or worldwide epidemic, that clearly fits the description of influenza was in 1580. At least four pandemics of influenza occurred in the 19th century, three in the 20th century, and one thus far in the 21st century. The pandemic of "Spanish" influenza in 1918–1919 caused an estimated 21 million deaths worldwide.

Wilson Smith, Christopher Andrewes, and Patrick Laidlaw isolated influenza A virus in ferrets in 1933, and Thomas Francis Jr. isolated influenza B virus in 1936. Also in 1936, Macfarlane Burnet discovered that influenza virus could be grown in embryonated hens' eggs. This led to the study of the virus's characteristics and the development and use of inactivated vaccines in the late 1930s and 1940s. The protective efficacy of these inactivated vaccines was demonstrated in the 1950s. The first live, attenuated influenza vaccine was licensed in 2003. A non-live, recombinant influenza virus vaccine not requiring isolation or growth in hen's eggs was licensed in 2013.

Influenza

- Viral illness
- First pandemic in 1580
- Estimated 21 million deaths worldwide in pandemic of 1918-1919
- Influenza A and B viruses isolated in the 1930s
- Inactivated vaccines first developed and used in the late 1930s and 1940s

Influenza Virus

Influenza is a single-stranded, helically shaped, RNA virus of the orthomyxovirus family. Three types of influenza virus are known to affect humans: A, B, and C. Type A influenza has subtypes determined by the surface antigens hemagglutinin (HA) and neuraminidase (NA). There are 18 different H subtypes and 11 different N subtypes. Eight H subtypes (H1, H2, H3, H5, H6, H7, H9, H10) and six N subtypes (N1, N2, N6, N7, N8, and N9) have been detected in humans. Type B influenza is classified into two lineages: B/Yamagata and B/Victoria.

Influenza Virus

- Single-stranded RNA virus
- Orthomyxovirus family
- Three types affect humans: A, B, C
- Infection can be asymptomatic or result in mild to severe disease

Infection with influenza viruses can be asymptomatic or result in disease that ranges from mild to severe. Influenza B more commonly affects children. Influenza C is rarely reported as a cause of human illness, probably because most cases are subclinical. Influenza C has not been associated with epidemic disease.

Antigenic Changes

Virus surface antigens hemagglutinin and neuraminidase continually change. Changes in influenza viruses can take the form of antigenic drift or antigenic shift.

Antigenic drift involves small mutations in the genes of influenza viruses that lead to changes in HA and NA that accumulate over time, resulting in the emergence of novel strains that the human immune system may not recognize. These novel strains are the influenza virus's evolutionary adaptations to a strong population-wide immune response.

Antigenic Changes

- Antigenic drift
  - Small mutations over time that result in novel strain
  - Primary reason people can get influenza more than once
  - May result in annual influenza epidemic
- Antigenic
  - Abrupt, major change in surface antigen(s)
  - May lead to pandemic (rare)

Antigenic drift is the primary reason people can get influenza more than once and why it is necessary to annually review and update the composition of influenza vaccines. Antigenic drift, along with waning immunity, results in annual influenza epidemics, since the protection that remains from past exposures to similar viruses is incomplete. Drift occurs in all three types of influenza virus (A, B, C).

Antigenic shift involves an abrupt, major change in one or both surface antigens (H or H-N combination). Antigenic shifts are probably due to genetic recombination (an exchange of a gene segment) between influenza A viruses that affect humans and/or animals. An antigenic shift may result in a worldwide pandemic if the virus is efficiently transmitted from person to person. Pandemics are rare; since the late 19th century, five antigenic shifts have led to pandemics in 1889-1891, 1918-1920, 1957-1958, 1968-1969, and 2009-2010.

Influenza Pathogenesis

- Respiratory transmission
- Replication in respiratory epithelium with subsequent destruction of cells
- Viremia rarely documented
- Virus shed in respiratory secretions for 5–10 days

Pathogenesis

Following respiratory transmission, the virus attaches to and penetrates respiratory epithelial cells in the trachea and bronchi. Viral replication occurs, which results in the destruction of the host cell. Regeneration of epithelium takes about 3 to 4 weeks. Viremia, or presence of virus in the blood, has rarely been documented. Virus is shed in respiratory secretions for 5 to 10 days, with a peak of 1 to 3 days following illness onset.

Influenza Clinical Features

- Incubation period 2 days (range, 1–4 days)
- About 8% of U.S. population gets sick each season
- Sudden onset of symptoms
  - Respiratory: cough, sore throat, runny or stuffy nose
  - Systemic: fever, chills, headache, malaise, myalgia
  - Gastrointestinal: vomiting, diarrhea
- Rapid recovery

Clinical Features

The incubation period for influenza is usually 2 days but can vary from 1 to 4 days. Influenza illness can range from asymptomatic to severe infection. On average, about 8% of the U.S. population gets sick from influenza each season (range between 3% and 11%).

Onset of influenza symptoms is sudden. Respiratory symptoms include cough, sore throat, and runny or stuffy nose. Systemic symptoms generally include fever, chills, headache, malaise, and myalgia. Vomiting and diarrhea may also occur, especially in children. Recovery is rapid; fever usually resolves within 3 to 4 days and other symptoms within approximately 7 days. Some patients may have lingering asthenia (lack of strength or energy) for several weeks. More information can be found at: www.cdc.gov/flu/symptoms/symptoms.htm.

Influenza symptoms (e.g., pain and fever) can be controlled with medications such as aspirin, ibuprofen, or acetaminophen. Aspirin and salicylate-containing products should not be used for children or adolescents because it may increase the risk for developing Reye syndrome.

Complications

People most at risk of developing serious influenza-related complications include people age 65 years and older, people with chronic medical conditions (e.g., heart disease or diabetes), pregnant women, and young children, especially those younger than age 2 years. More common complications of influenza include secondary bacterial pneumonia (e.g., *Streptococcus pneumoniae, Haemophilus influenzae*, or *Staphylococcus aureus*), exacerbations of underlying respiratory conditions, otitis media, laryngotracheobronchitis, and bronchitis.

Other complications may include primary pneumonia, encephalitis, aseptic meningitis, transverse myelitis, myocarditis, pericarditis, Guillain-Barré syndrome, and Reye Syndrome. Reye syndrome is a complication that occurs almost exclusively in children taking aspirin, primarily in association with influenza B virus (or varicella zoster virus), and presents with severe vomiting and confusion, which may progress to coma due to swelling of the brain.

Most deaths due to influenza typically occur among persons age 65 years and older.

Influenza Complications

- Secondary bacterial pneumonia
- Exacerbations of underlying respiratory conditions
- Otitis media
- Laryngotracheobronchitis
- Bronchitis
- Other less common complications may occur

Laboratory Testing

Influenza is usually suspected based on characteristic clinical findings, particularly if influenza has been reported in the community. Influenza virus testing is not required to make a clinical diagnosis but can inform clinical management when results may influence decisions to initiate antiviral treatment, perform other diagnostic testing, or implement infection and prevention control measures. Diagnostic tests include:

- Molecular assays (i.e., rapid molecular assays, reverse transcription polymerase chain reaction (RT-PCR), and other nucleic acid amplification tests)
- Antigen detection tests (i.e., rapid influenza diagnostic tests and immunofluorescence assays)

Approved respiratory tract specimens differ among the FDA-cleared influenza tests, so clinicians should refer to the specific test's package insert for approved respiratory specimens.

In addition to diagnostic testing for only influenza virus, the Flu SC2 Multiplex Assay is a real-time RT-PCR test that detects and differentiates RNA from SARS-CoV2, influenza A virus, and influenza B virus in upper or lower respiratory specimens.

Serology testing is no longer used for clinical diagnosis of influenza but is still used for research studies.

Information for health care providers on influenza virus testing can be found at www.cdc.gov/flu/professionals/diagnosis/index.htm. Details about the laboratory diagnosis of influenza are available at www.cdc.gov/flu/symptoms/testing.htm.

Medical Management

Vaccination is the principal means for preventing influenza-related morbidity and mortality, however antiviral agents may be indicated in some situations for preventing and/or treating influenza. Current recommendations and a decision tree for clinicians is available for making antiviral decisions: https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

Influenza Epidemiology

- Reservoir
  - Type A infects humans and some animals
  - Type B generally infects humans
  - Type C infects only humans
- Transmission
  - Person-to-person via large droplets
  - Aerosol transmission of small droplets
  - Exposure to fomites
- Temporal pattern
  - October–April or May in northern hemisphere
  - April–September in southern hemisphere
  - Year round in tropical climates
- Communicability
  - 1 day before to 5 to 7 days after (adults) or 10 days after onset (children)

Epidemiology

Occurrence

Influenza occurs throughout the world.

Reservoir

Humans are the only known reservoir of influenza type C. Influenza B generally infects humans, but at least two reports have documented influenza B in seals. Influenza A viruses may infect both humans and some animals. Examples of animals include, but are not limited to, wild birds, poultry, pigs, horses, mink, and ferrets. There is no chronic carrier state.

Transmission

Influenza is primarily transmitted from person to person via large, virus-laden droplets (more than 5 microns in diameter) that are generated when infected persons cough or sneeze. These large droplets can then settle on the mucosal surfaces of the upper respiratory tracts of susceptible persons who are within six feet of infected persons. Aerosol transmission of small droplets may also transmit influenza. Transmission may occur through direct or indirect contact with respiratory secretions, such as when touching surfaces contaminated with influenza virus and then touching the eyes, nose, or mouth.

Temporal Pattern

In the Northern Hemisphere, influenza season can begin as early as October and last as late as April or May, while in the Southern Hemisphere, the season typically occurs during April-September. Influenza occurs throughout the year in tropical areas. In the United States, for 75% of influenza seasons from the 1982–1983 through the 2017–2018 season, peak influenza activity has not occurred until January or later. In 58% of seasons, the peak was in February or later.

Communicability

Adults can transmit influenza from the day before symptom onset to approximately 5 to 7 days after symptoms begin. Children can transmit influenza to others for 10 or more days after symptoms begin.

Secular Trends in the United States

Symptomatic illness of influenza is common. CDC estimates that between 9.3 million and 45 million people experience symptomatic illness annually. An increase in mortality typically accompanies each annual influenza season. Increased mortality results not only from influenza and pneumonia, but also from cardiopulmonary and other chronic diseases that can be exacerbated by influenza.

The number of influenza-associated deaths varies substantially by year, influenza virus type and subtype, and age group. Since 2010, CDC estimates the number of annual influenza-associated deaths has ranged from a low of 12,447 (2011–2012 season) to a high of 61,099 (2017–2018 season), with an average of 37,463 influenza-associated deaths annually. Persons age 65 years and older account for approximately 80% of deaths attributed to influenza. While relatively rare, some children die from influenza each year. The 2019-2020 influenza season marked the highest recorded number for pediatric influenza deaths during a regular season at 189 reported pediatric influenza deaths.

The risk for complications and hospitalizations from influenza is higher among persons age 65 years and older, pregnant and post-partum women, children younger than age 5 years, and persons of any age with certain underlying medical conditions. Since 2010, an average of more than 445,000 hospitalizations per year have been related to influenza, with about 38% occurring in persons younger than age 65 years.

Influenza causes more hospitalizations among young children than any other vaccine-preventable disease. CDC estimates that since 2010, influenza-related hospitalizations among U.S. children younger than age 5 years have ranged from 7,000 to 26,000 each year. Healthy children age 5 through 18 years are not at increased risk for influenza complications. However, children typically have the highest attack rates during community outbreaks of influenza and serve as a major source of influenza transmission within communities.

During the 2019–2020 influenza season, 75.5% of children age 6 months–4 years and 64.6% of children age 5–12 years received the influenza vaccine. Coverage was 53.3% for adolescents age 13 through 17 years. Among adults age 18 through 64 years and age 65 years and older, 42.3% and 69.8% received the influenza vaccine, respectively. Coverage in all age groups increased from the 2018–2019 season, with the largest increase (3.3%) in adults

Influenza Secular Trends in the United States

- 9.3 to 45 million people experience symptomatic illness annually
- Annual average of 37,463 influenza-associated deaths since 2010
- Groups at risk for complications and hospitalizations include:
  - Persons age 65 years and older
  - Pregnant and post-partum women
  - Children younger than age 5 years
  - Persons with certain underlying medical conditions
- Causes more hospitalization among young children than any other vaccine-preventable disease

age 18 through 64 years. During 2019–2020, 61.2% of pregnant women received influenza vaccination.

CDC estimates that vaccination in the U.S. during 2010–2011 through 2017–2018 seasons averted an estimated 4.9 million symptomatic illnesses, 2.4 million medical visits, 70,000 hospitalizations, and 6,400 deaths. Adults age 65 years represented a majority of the averted deaths (80%) and hospitalizations (58%). Children age 6 months to 17 years represented 43% of averted symptomatic illness and 51% of averted medical visits.

Pandemics

Since the late 19th century, five antigenic shifts have led to pandemics. Typically during influenza pandemics, there are high attack rates involving all age groups, and mortality is usually markedly increased. Severity is generally not greater in the individual patient (except for during the 1918–1919 pandemic), but because large numbers of persons are infected, there will be a large number of severe and fatal cases. Onset may occur in any season of the year. Secondary and tertiary waves may occur up to two years later, usually in the winter.

In January 2011, CDC estimated that the 2009 H1N1 caused illness in more than 60 million Americans, leading to more than 270,000 hospitalizations and 12,500 deaths. Contrary to typical seasons, ninety percent of hospitalizations and deaths occurred in persons younger than age 65 years.

Influenza Vaccines

- Vaccine composition reviewed and updated each year, for current information see: https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/flu.html
  - Inactivated influenza vaccine (IIV)
  - Live, attenuated influenza vaccine (LAIV)
  - Recombinant influenza vaccine (RIV)

Influenza Vaccines

Vaccine composition is reviewed and updated each year since the influenza virus is constantly changing. Considerations include which influenza viruses are causing illness, the extent to which viruses are spreading, and how well the previous season's vaccine protects against those viruses.

Three types of influenza vaccine are available in the United States: inactivated influenza vaccine (IIV); live, attenuated influenza vaccine (LAIV); and recombinant influenza vaccine (RIV). Trivalent vaccine contains three inactivated viruses: type A(H1N1), type A(H3N2), and type B. Quadrivalent influenza vaccines were first introduced during the 2013–2014 season. They contain the same antigens as trivalent vaccines, with an additional type B strain.

ACIP does not recommend use of any influenza vaccine outside the vaccine's FDA-approved age indication. Information about current influenza vaccines and recommendations from the Advisory Committee on Immunization Practices (ACIP) are updated annually. For current information, see https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/flu.html.

Characteristics

Inactivated Influenza Vaccines (IIV)

IIV has been available since the 1940s. Most influenza vaccines distributed in the United States are subvirion (split-virus) or subunit inactivated vaccines. IIV currently licensed and distributed in the United States is administered by the intramuscular route. Vaccines are available in multiple presentations (manufacturer-filled syringe, single-dose vials, and multidose vials) and in preservative-free formulations. Viruses for IIV are grown in either chicken eggs (egg-based) or cell culture (cell culture-based). The final products from egg-based IIV contain residual egg protein. Thimerosal may be used in some influenza vaccines as a preservative to prevent microbial growth. The FDA package inserts can be referenced annually for the most current influenza vaccine ingredients.

Recombinant Influenza Vaccine (RIV)

RIV was first approved for use in 2013. The RIV manufacturing process uses recombinant DNA technology and does not require an egg-grown vaccine virus. The resulting vaccine contains recombinant hemagglutinin.

Live, Attenuated Influenza Vaccine (LAIV)

LAIV was first approved for use in the United States in 2003. The vaccine viruses are grown in chicken eggs and the final product contains residual egg protein. The viruses are cold-adapted and replicate effectively in the mucosa of the nasopharynx. LAIV is administered intranasally. The vaccine is provided in a manufacturer-filled, single use, intranasal sprayer; half of the dose is sprayed into each nostril. Vaccinated children can shed vaccine viruses in nasopharyngeal secretions for up to 3 weeks. Transmission of shed LAIV viruses from vaccine recipients to unvaccinated persons has been documented but has not been reported to be associated with serious illness.

Influenza Vaccine Characteristics

- IIV
  - Administered by intramuscular injection
  - Multidose vials contain thimerosal
  - Some products contain residual egg protein
- RIV
  - Administered by intramuscular injection
  - Does not contain egg protein
- LAIV
  - Administered intranasally
  - Contains residual egg protein

Vaccination Schedule and Use

Influenza vaccination is recommended annually for persons age 6 months and older who do not have contraindications. Vaccination is particularly important for persons at increased risk for severe illness and complications from influenza. When vaccine supply is limited, efforts should focus on delivering vaccination to high-risk groups who do not have contraindications. Emphasis should also be placed on vaccination of persons who live with or care for those who are at increased risk (e.g., healthcare personnel).

Influenza activity can begin as early as October and last as late as April or May, but most frequently peaks in January. To ensure maximum protection, vaccination should be administered before the onset of influenza activity in the community.

Influenza Vaccination Schedule

- 1 dose each influenza season for persons age 9 years or older
- 1 or 2 doses each influenza season for children age 6 months through 8 years
  - 1 dose if 2 or more doses are documented prior to July 1
  - 2 doses administered at least 4 weeks apart if 2 or more doses are not documented prior to July 1
- Refer to ACIP recommendations each season for most recent schedule

However, varied timing of onset, peak, and duration of influenza season, as well as potential vaccine-induced immunity waning, make it difficult to determine the ideal time to administer vaccine for each season. CDC recommends influenza vaccination by the end of October. However, vaccine should continue to be offered throughout the influenza season, even into January or later. Getting vaccinated early (e.g., July or August) is likely to be associated with reduced protection against influenza infection later in the influenza season, particularly among older adults.

IIV and RIV should be administered by intramuscular injection. Both IIV and RIV may be administered on the same day or any time before or after other inactivated vaccines or live vaccines. If given on the same day with other injectable vaccines, the vaccines should be administered at separate anatomic sites. LAIV should be administered intranasally. It may be given on the same day with other live or inactivated vaccines. If LAIV is not administered on the same day with other live vaccines, then at least 4 weeks should separate administration of LAIV and other live vaccines.

Persons age 9 years or older should receive 1 dose of a licensed age-appropriate vaccine each influenza season. Children age 6 months through 8 years who do not have documentation showing receipt of 2 or more doses of any influenza vaccine prior to July 1 should receive 2 doses of a licensed age-appropriate vaccine. This 2-dose series should be administered at least 4 weeks apart.

Influenza Vaccine Efficacy

- Duration of immunity less than one year due to waning and antigenic drift
- 40% to 60% effective in reducing the risk of influenza
  - Effectiveness depends on similarity of vaccine strain(s) to circulating strain(s), age and health status of recipient, and type of vaccine administered

Immunogenicity and Vaccine Efficacy

For practical purposes, the duration of immunity following influenza vaccination is less than one year because of vaccine-induced antibody waning and antigenic drift of circulating influenza viruses. Influenza vaccine effectiveness depends on many factors including the similarity of the vaccine strain(s) to the circulating strain(s), the age and health status of the recipient, and the type of vaccine administered. Vaccination is effective in reducing the risk of influenza illness by 40% to 60% in the overall population when vaccine strains and circulating viruses are similar. However, the vaccine can be less effective in preventing illness among persons age 65 years and older.

During the 2010–2011 to 2018–2019 influenza seasons, adjusted overall vaccine efficacy has ranged from 19% to 60% in patients age 6 months and older. Circulating A/H3N2 influenza viruses drifted significantly after strain selection for the 2014–2015 vaccines, contributing to a lower vaccine efficacy of 19% during that season.

Studies have demonstrated a variety of benefits to influenza vaccination, including fewer: Illnesses, medical visits, ICU and hospital admissions, and days in the ICU and hospital. Fewer

deaths have been demonstrated only in children. Additionally, some studies show that severity of illness among vaccinated persons who become sick is reduced. Influenza vaccination has also been associated with positive outcomes for people with chronic health conditions (e.g., lower rates of cardiac events among people with heart disease) and pregnant women (e.g., reduced risk of hospitalization and acute respiratory infection).

A number of influenza vaccines from different manufacturers are available each season. Where there is more than one influenza vaccine available that is appropriate for a given recipient, ACIP does not express a preference for any one vaccine over another.

Contraindications and Precautions to Vaccination

Inactivated Influenza Vaccine (IIV) and Recombinant Influenza Vaccine (RIV)

As with other vaccines, a history of severe allergic reaction (anaphylaxis) to a vaccine component or following a prior dose is a contraindication to further doses. Moderate or severe acute illness (with or without fever) in a patient is considered a precaution to vaccination, although persons with minor illness may be vaccinated.

History of Guillain-Barré syndrome within 6 weeks of receipt of influenza vaccine is a precaution to vaccination for all influenza vaccines licensed in the United States.

Because vaccine composition is reviewed and updated each year, refer to ACIP's most recent recommendations for contraindications and precautions: https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/flu.html.

Influenza Vaccine Contraindications and Precautions (IIV and RIV)

- Contraindication
  - Severe allergic reaction to vaccine component or following a prior dose
- Precaution
  - Moderate or severe acute illness
  - History of Guillain-Barré syndrome (GBS) within 6 weeks of receipt of influenza vaccine
- Refer to ACIP influenza vaccine recommendations for LAIV contraindications and precautions

Live, Attenuated Influenza Vaccine (LAIV)

LAIV has additional contraindications and precautions. Refer to ACIP's most recent recommendations for LAIV contraindications and precautions: https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/flu.html.

Vaccine Safety

Inactivated Influenza Vaccine (IIV)

Studies support the safety of annual IIV vaccination in children and adults. Local reactions are the most common adverse reactions following vaccination with IIV. These include soreness, redness, tenderness, or swelling at the injection site. These reactions are transient, generally lasting 1 to 2 days. In clinical trials, pain at the injection site during the first week after vaccination occurred in up to 65% of people vaccinated with IIV.

Influenza Vaccine Safety

IIV

- Soreness, redness, tenderness, or swelling at the injection site is common
- No clear link with GBS; risk would be no more than 1 to 2 cases per million

RIV

- Tenderness
  - 48%
- Pain
  - 37%
- Headache
  - 20%
- Fatigue
  - 17%
- Muscle pain
  - 13%

LAIV

- Runny nose, nasal congestion (children)
- Sore throat, headache, tiredness/weakness, muscle aches, cough, chills, sinusitis (adults)

Nonspecific systemic symptoms, including fever, chills, malaise, and myalgia, occur less often. These symptoms usually occur in those with no previous exposure to the viral antigens in the vaccine. Symptoms usually occur within 6 to 12 hours of IIV vaccination and last 1 to 2 days. Recent reports indicate systemic symptoms are no more common after receipt of IIV than in persons given a placebo injection.

In some influenza seasons, IIV has been associated with an increased risk for febrile seizures on the day of, and the day after vaccination in young children. Febrile seizure is more likely to occur if IIV is given on the same day as 13-valent pneumococcal conjugate vaccine (PCV13) and diphtheria, tetanus, and acellular pertussis (DTaP) vaccines. Most febrile seizures are brief and have a good prognosis. ACIP reviewed the risks and benefits of febrile seizures after IIV and did not make any changes in the recommendations for administering pediatric vaccines; these vaccines can be given on the same day.

Guillain-Barré syndrome (GBS), a serious neurological condition that can cause paralysis, is known to occur after multiple infectious illnesses, particularly gastrointestinal and upper respiratory infections. GBS is known to occur rarely after influenza illness. Safety monitoring of seasonal IIV over the course of many years has not detected a clear link to GBS. If there is a risk of GBS from IIV, it would be no more than 1 to 2 cases per million people vaccinated. Studies suggest that the risk of GBS after influenza illness is higher than the potential risk of developing GBS after vaccination.

Recombinant Influenza Vaccine (RIV)

Studies support the safety of RIV in adults. During the pre-licensure clinical trials for RIV, the most common injection-site reaction for adults age 18 through 49 years were tenderness (48%) and pain (37%); the most common solicited systemic adverse reactions were headache (20%), fatigue (17%), and muscle pain (13%). Two serious adverse events (pleuropericarditis and vasovagal syncope) were assessed as possibly related to RIV vaccination. After licensure, a review of reports to the Vaccine Adverse Event Reporting System (VAERS) from 2013–2016 found 88 reports; allergic reactions were the most common adverse event reported. Other adverse events reported were injection site reactions, fatigue, myalgia, headache, and fever. There were four serious reports but no death was reported.

Live, Attenuated Influenza Vaccine (LAIV)

Studies support the safety of LAIV. In pre-licensure clinical trials, the most common adverse reactions were runny nose or nasal congestion in all ages, fever in children age 2 through 6 years, and sore throat in adults. Clinical trials show LAIV4 has a safety

profile similar to the previously used trivalent LAIV, with the exception of slightly more reports of fever after the first dose of LAIV4 compared to trivalent LAIV in children age 2 through 8 years who were getting vaccinated for the first time. In adults, other adverse events reported more often after LAIV than after placebo were headache, sore throat, tiredness/weakness, muscles aches, cough, chills, and sinusitis.

Limited data are available concerning the safety of LAIV among persons at high risk for influenza complications, such as immunosuppressed persons or those with chronic pulmonary or cardiac disease. Therefore, persons at high risk of influenza complications should receive IIV rather than LAIV.

Vaccination During Pregnancy

Pregnant women are at an increased risk for severe illness and complications from influenza due to changes in immunologic, heart and lung function. In addition, some studies suggest influenza infection is associated with preterm delivery and fetal demise. ACIP and the American College of Obstetricians & Gynecologists recommend women who are pregnant, might be pregnant, or are up to two weeks postpartum during the influenza season should receive any licensed, age-appropriate IIV or RIV product. LAIV is contraindicated during pregnancy. Vaccination can occur at any time during pregnancy, before and during the influenza season.

Vaccine Storage and Handling

Influenza vaccines (IIV, RIV, and LAIV) should be maintained at refrigerator temperature between 2°C and 8°C (36°F and 46°F). LAIV sprayers must be kept in the carton until use in order to protect from light. For complete information on best practices and recommendations, please refer to CDC's Vaccine Storage and Handling Toolkit, www.cdc.gov/vaccines/hcp/admin/storage/toolkit/storage-handling-toolkit.pdf.

Surveillance and Reporting of Influenza

Influenza-associated deaths among children younger than age 18 years and human infection with a novel influenza A virus are nationally notifiable conditions reported through the National Notifiable Diseases Surveillance System (NNDSS). Other influenza virus infections are not nationally notifiable but may be reported in some states. Influenza surveillance in the U.S. consists of five categories of information, including viral, outpatient illness, mortality, and hospitalization surveillance, as well as summary of the geographic spread of influenza.

Influenza surveillance is intended to monitor the prevalence of circulating strains and detect new strains necessary for vaccine formulation; estimate influenza-related impact on morbidity,

NOTES

mortality, and economic loss; rapidly detect outbreaks; and assist disease control through rapid preventive action (e.g., chemoprophylaxis of unvaccinated high-risk patients).

For information on guidance for state and local health department staff who are involved in surveillance activities for vaccine-preventable diseases, please consult the Manual for the Surveillance of Vaccine-Preventable Diseases, www.cdc.gov/vaccines/pubs/surv-manual/chapters.html.

Acknowledgements

The editors would like to acknowledge Scott Epperson, Lisa Grohskopf, David Shay, Tom Shimabukuro, and Jerome Tokars for their contributions to this chapter.

Selected References

American Academy of Pediatrics. Influenza. In: Kimberlin D, Brady M, Jackson M, et al., eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:476–90.

Arriola C, Garg S, Anderson E, et al. Influenza Vaccination Modifies Disease Severity Among Community-dwelling Adults Hospitalized With Influenza. *Clin Infect Dis* 2017;65(8):1289–97.

Boni M. Vaccination and antigenic drift in influenza. *Vaccine* 2008;26(Suppl 3):C8–14.

Bresee J, Fry A, Sambhara S, et al. Inactivated influenza vaccines. In: Plotkin S, Orenstein W, Offit P, et al., eds. *Plotkin's Vaccines*. 7th ed. Elsevier;2018:456–88.

CDC. Disease Burden of Influenza. https://www.cdc.gov/flu/about/burden/index.html. Accessed October 23, 2020.

CDC. FluVaxView Interactive!. https://www.cdc.gov/flu/fluvaxview/interactive.htm. Accessed October 15, 2020.

CDC. Influenza vaccination of health-care personnel. Recommendations of the Healthcare Infection Control Practices Advisory Committee (HICPAC) and the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2006;55(No. RR02):1–16.

CDC. Past Seasons Vaccine Effectiveness Estimates. https://www.cdc.gov/flu/vaccines-work/past-seasons-estimates.html. Accessed October 23, 2020.

CDC. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices—United States, 2019–20. *MMWR* 2019;68(3):1–21.

CDC. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices—United States, 2017–18 influenza season. *MMWR* Recomm Rep 2017;66(2):1–22.

CDC. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices–United States, 2020-21 influenza season. *MMWR* 2020;69(8):1–24.

CDC. Seasonal Influenza Vaccine Safety: A Summary for Clinicians. https://www.cdc.gov/flu/professionals/vaccination/vaccine_safety.htm. Accessed October 26, 2020.

Duffy J, Weintraub E, Hambidge S. Febrile seizure risk after vaccination in children 6 to 23 months. *Pediatrics* 2016;130(1):e20160320.

Ferdinands J, Olsho L, Agan A, et al. Effectiveness of Influenza Vaccine Against Life-threatening RT-PCR-confirmed Influenza Illness in US Children, 2010–2012. *J Infect Dis* 2014;210(5):674–83.

Jhung M, Swerdlow D, Olsen S, et al. Epidemiology of 2009 pandemic influenza A (H1N1) in the United States. *Clin Infect Dis* 2011;52(suppl 1):S13–26.

Luke C, Lakdawala S, Subbarao K. Influenza vaccine–live. In: Plotkin S, Orenstein W, Offit P, et al., eds. Plotkin's *Vaccines*. 7th ed. Elsevier;2018:489–510.

Monto A, Ohmit S, Petrie J, et al. Comparative efficacy of inactivated and live attenuated influenza vaccines. *N Engl J Med* 2009;361:1260–7.

Murphy K, Strunk R. Safe administration of influenza vaccine in asthmatic children hypersensitive to egg protein. *J Pediatr* 1985;106(6):931–3.

Razzaghi H, Kahn K, Black C, et al. Influenza and Tdap vaccination coverage among pregnant women — United States, April 2020. *MMWR* 2020;69(39):1391–7.

Rondy M, Omeiri N, Thompson M, et al. Effectiveness of influenza vaccines in preventing severe influenza illness among adults: A systematic review and meta-analysis of test-negative design case-control studies. *J Infect* 2017;75(5):381–94.

Rongxia L, Stewart B, McNeil M. Post licensure surveillance of influenza vaccines in the Vaccine Safety Datalink in the 2013-2014 and 2014-2015 seasons. *Pharmacoepidemiol Drug Saf* 2016;25(8):928–34.

NOTES

NOTES

Thompson M, Kwong J, Regan A, et al. Influenza Vaccine Effectiveness in Preventing Influenza-associated Hospitalizations During Pregnancy: A Multi-country Retrospective Test Negative Design Study, 2010–2016. *Clin Infect Dis* 2019;68(9):1444–53.

Thompson M, Pierse N, Huan Q, et al. Influenza vaccine effectiveness in preventing influenza-associated intensive care admissions and attenuating severe disease among adults in New Zealand 2012–2015. *Vaccine* 2018;36(39):5916–25.

Treanor J, Talbot H, Ohmit S, et al. Effectiveness of seasonal influenza vaccines in the United States during a season with circulation of all three vaccine strains. *Clin Infect Dis* 2012;55(7):951–9.

Treanor J. Influenza viruses. In: Kaslow R, Stanberry L, Le Duc J, eds. *Viral Infections of Humans Epidemiology and Control*. 5th edition. Boston, MA: Springer;2014:455–78.

Udell J, Zawi R, Bhatt D, et al. Association between influenza vaccination and cardiovascular outcomes in high-risk patients: a meta-analysis. *JAMA* 2013;310(16):1711–20.

Walter E, Klein N, Wodi A. Fever after influenza, diphtheria-tetanus-acellular pertussis, and pneumococcal vaccinations. *Pediatrics* 2020;145(3):e20191909.

Zimmerman R, Nowalk M, Chung J, et al. 2014-2015 influenza vaccine effectiveness in the United States by vaccine type. *Clin Infect Dis* 2016;63(12):1564–73.

Woo EJ, Moro PL, Cano M, Jankosky C. Postmarketing safety surveillance of trivalent recombinant influenza vaccine: Reports to the Vaccine Adverse Event Reporting System. *Vaccine*. 2017;35(42):5618–21.

Paul Gastanaduy, MD; Penina Haber, MPH; Paul A. Rota, PhD; and Manisha Patel, MD, MS

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

In 1846, Peter Panum described the incubation period of measles and lifelong immunity after recovery from the disease. John Enders and Thomas Chalmers Peebles isolated the virus in human and monkey kidney tissue culture in 1954. The first live, attenuated vaccine (Edmonston B strain) was licensed for use in the United States in 1963. In 1971, a combined measles, mumps, and rubella (MMR) vaccine was licensed for use in the United States. In 2005, a combination measles, mumps, rubella, and varicella (MMRV) vaccine was licensed.

Before a vaccine was available, infection with measles virus was nearly universal during childhood, and more than 90% of persons were immune due to past infection by age 15 years. Measles is still a common and often fatal disease in developing countries. The World Health Organization estimates there were 142,300 deaths from measles globally in 2018. In the United States, there have been recent outbreaks; the largest occurring in 2019 primarily among people who were not vaccinated.

Measles

- Acute viral infectious disease
- First described in 7th century
- Vaccines first licensed include measles in 1963, MMR in 1971, and MMRV in 2005
- Infection nearly universal during childhood in prevaccine era
- Still common and often fatal in developing countries

Measles Virus

The measles virus is a paramyxovirus of the genus *Morbillivirus*. It is 120 to 250 nm in diameter, with a genome of single-stranded, negative sense 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 binding of virus to receptors on host cells.

There is only one antigenic type of measles virus. Although studies have documented antigenic changes in the H protein, 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, sunlight, acidic pH, ether, and trypsin.

Measles Virus

- Paramyxovirus (RNA)
- F (fusion) protein fuses virus and host cell members and H (hemagglutinin) protein binds virus to host receptors
- One antigenic type
- Rapidly inactivated by heat, sunlight, acidic pH, ether, and trypsin

Pathogenesis

Measles is a systemic infection. The primary site of infection is alveolar macrophages or dendritic cells. Two to three days after replication in the lung, measles virus spreads to regional lymphoid tissues followed by a systemic infection. Following further viral replication in regional and distal reticuloendothelial

Measles Pathogenesis

- Primary site of infection is alveolar macrophages or dendritic cells
- Primary viremia 2 to 3 days after replication
- Secondary viremia 5 to 7 days after exposure

sites, a second viremia occurs 5 to 7 days after initial infection. During this phase, infected lymphocytes and dendritic cells migrate into the subepithelial cell layer and transmit measles to epithelial cells. Following amplification in the epithelia, the virus is released into the respiratory tract.

Measles Clinical Features

- Incubation period 11 to 12 days
  - Exposure to rash onset averages 14 days (range, 7 to 21 days)
- Prodrome lasts 2 to 4 days (range, 1 to 7 days)
  - Stepwise increase in fever to 103°F–105°F
  - Cough, coryza, and conjunctivitis
  - Koplik spots (on mucous membranes)
- Rash
  - Persists 5 to 6 days
  - Begins at hairline, then involves face and upper neck
  - Proceeds downward and outward to hands and feet
  - Severe areas peel off in scales
  - Fades in order of appearance

Measles Complications

- Diarrhea, otitis media, pneumonia, encephalitis, subacute sclerosing panencephalitis, death
- Most common among children younger than age 5 years and adults

Clinical Features

The incubation period of measles from exposure to prodrome averages 11 to 12 days. The time from exposure to rash onset averages 14 days, with a range of 7 to 21 days.

The prodrome lasts 2 to 4 days, with a range of 1 to 7 days. It is characterized by fever, which increases in a stepwise fashion often peaking as high as 103°F to 105°F, cough, coryza, and conjunctivitis.

Koplik spots, present on mucous membranes, are considered to be unique to measles. They occur 1 to 2 days before the measles rash (i.e., during the prodromal period), and appear as punctate blue-white spots on the bright red background of the buccal mucosa.

The measles rash is a maculopapular eruption that usually lasts 5 to 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 individually distinct but may run together, particularly on the upper body. Initially, lesions blanch (become white or pale) with fingertip pressure. By 3 to 4 days, most do not blanch with pressure. The lesions peel off in scales in more severely involved areas. The rash fades in the same order that it appears, from head to extremities.

Other symptoms of measles include anorexia and generalized lymphadenopathy.

Complications

Approximately 30% of measles cases in the United States from 1987 to 2000 were reported to have one or more complications. Complications include diarrhea, otitis media, pneumonia, encephalitis, subacute sclerosing panencephalitis, and death. Complications of measles were most common among children younger than age 5 years and adults.

Laboratory Testing

The most widely used methods for laboratory confirmation of measles are detection of measles virus RNA in nasopharyngeal aspirates, throat swabs, or urine by reverse transcriptase polymerase chain reaction (RT-PCR) or detection of measles specific IgM in serum samples by enzyme immunoassay (EIA).

Collection of both a throat swab specimen for RT-PCR and a serum specimen for IgM detection is recommended from all patients with clinical features compatible with measles.

Clinical specimens for viral detection should be collected at the same time as samples taken for serologic testing. In addition to RT-PCR for diagnosis, viral genotyping performed by state public health laboratories or CDC can help to track the transmission pathways of measles virus. Specimens for viral detection should be shipped to a state public health laboratory or CDC (at the direction of the state health department).

Laboratory testing can confirm the presence of measles vaccine virus in a recently vaccinated and potentially exposed individual.

Epidemiology

Occurrence

Measles occurs throughout the world. Interruption of indigenous transmission of measles was declared in the United States in the year 2000 and in other parts of the Western Hemisphere in 2016. However, outbreaks with sustained measles virus transmission have recently occurred in Venezuela and Brazil, leading to re-establishment of endemic transmission in these countries and loss of measles elimination in the Americas.

Reservoir

Measles is a human disease. There is no known animal reservoir, and an asymptomatic carrier state has not been documented.

Transmission

Measles transmission occurs person-to-person via large respiratory droplets and via airborne transmission of aerosolized droplet nuclei in closed areas (e.g., an office examination room) for up to 2 hours after a person with measles occupied the area.

Temporal Pattern

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

Communicability

Measles is highly communicable, with more than 90% secondary attack rates among exposed susceptible persons in close-contact settings. Measles is considered transmissible from 4 days before through 4 days after rash onset.

Measles Epidemiology

- Reservoir
  - Human
- Transmission
  - Person-to-person via large respiratory droplets
  - Airborne in closed areas for up to 2 hours
- Temporal pattern
  - Primarily late winter and spring
- Communicability
  - 4 days before through 4 days after rash onset

Measles Secular Trends in the United States

- About 500,000 reported cases and 500 deaths annually before vaccine
  - Actual cases estimated at 3 to 4 million
- Following vaccine licensure in 1963, incidence decreased by over 95%
- Measles occurrence among vaccinated school-aged children in the 1980s led to recommendations for a second dose
- In 2019, 13 outbreaks reported; underimmunized communities accounted for 88% of cases

Secular Trends in the United States

Before 1963, approximately 500,000 cases and 500 measles deaths were reported annually, with epidemic cycles every 2 to 3 years. However, the actual number of cases was estimated at 3 to 4 million annually. More than 50% of persons had measles by age 6 years, and more than 90% by age 15 years. In the years following licensure of vaccine in 1963, the incidence of measles decreased by more than 95%, and 2- to 3-year epidemic cycles no longer occurred. From 1985 through 1988, 68% of cases in school-aged children (age 5 to 19 years) occurred among those who had been appropriately vaccinated – i.e., had received a single dose of measles vaccine as recommended. The occurrence of measles among previously vaccinated children (i.e., vaccine failure) led to a recommendation for a second dose in this age group in 1989.

In 2019, 13 outbreaks of measles were reported, accounting for 663 cases; six were associated with underimmunized close-knit communities and accounted for 88% of all cases. Before 2019, the highest number of measles cases following elimination in the United States occurred in 2014 when 667 cases were reported. Increasing incidence of measles globally contributes to increased opportunities for measles importation into the United States. Fortunately, public health measures and a long-standing vaccination program has prevented outbreaks form imported cases.

Among children born during 2016–2017, 90.7% received measles, mumps, and rubella-containing vaccine by age 24 months; this was not statistically significantly different from the coverage of 90.3% for children born during 2014–2015.

Measles Vaccines

- MMR (MMR-II)
- MMRV (ProQuad)

Measles Vaccines

In 1963, both an inactivated ("killed") and a live, attenuated (Edmonston B strain) measles vaccine were licensed for use in the United States. The inactivated vaccine was withdrawn in 1967 because it did not protect well against measles. 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 (Schwarz strain) vaccine was first introduced in 1965, but also is no longer used in the United States. Another live, further attenuated strain (Edmonston-Enders strain) vaccine was licensed in 1968. These further attenuated vaccines caused fewer reactions than the original Edmonston B vaccine. In 1971, measles vaccine was licensed as a combined measles, mumps, and rubella (MMR) vaccine. In 2005, a combination measles, mumps, rubella, and varicella (MMRV) vaccine was licensed.

Measles vaccine is available as measles, mumps, and rubella vaccine (MMR [MMR-II]) and measles, mumps, rubella, and varicella vaccine (MMRV [ProQuad]). Both MMR and MMRV

vaccine contain live, attenuated viruses. Single-antigen measles vaccine is not available in the United States. The Advisory Committee on Immunization Practices (ACIP) recommends that MMR or MMRV vaccine be used when any of the individual components is indicated.

Characteristics

MMR vaccine is a lyophilized preparation of measles virus vaccine live, an attenuated line of measles virus, derived from Enders' attenuated Edmonston strain and propagated in chick embryo cell culture; mumps virus vaccine live, the Jeryl Lynn strain of mumps virus propagated in chick embryo cell culture; and rubella virus vaccine live, the Wistar RA 27/3 strain of live attenuated rubella virus propagated in WI-38 human diploid lung fibroblasts. MMRV vaccine contains measles, mumps, and rubella virus of equal titer and identical to those in the MMR vaccine. The titer of Oka varicella zoster virus is higher in MMRV vaccine than in single-antigen varicella vaccine, a minimum of 9,772 plaque-forming units (PFU) versus 1,350 PFU, respectively. MMR and MMRV vaccines are supplied as a lyophilized (freeze-dried) powder and are reconstituted with sterile, preservative-free water. Both vaccines contain gelatin. MMR and MMRV vaccines are administered by the subcutaneous route. Each dose of MMR and MMRV vaccine contains neomycin as an antibiotic. It contains no adjuvant or preservative.

Measles Vaccine Characteristics

- Live, attenuated vaccine
- Available as lyophilized powder and reconstituted with sterile, preservative-free water
- Administered by subcutaneous injection
- Contains gelatin
- Contains neomycin

Vaccination Schedule and Use

MMR vaccine or MMRV vaccine can be used to implement the vaccination recommendations for prevention of measles, mumps, and rubella. MMR vaccine is licensed for use in persons age 12 months or older. MMRV vaccine is licensed for use in persons age 12 months through 12 years; MMRV vaccine should not be administered to persons age 13 years or older.

Two doses of MMR vaccine, separated by at least 4 weeks, are routinely recommended for children age 12 months or older. Dose 1 of MMR vaccine should be given at age 12 through 15 months. A second dose of MMR vaccine is recommended based on previous observations of the failure of some to generate an immune response to measles following dose 1. Dose 2 is routinely given at age 4 through 6 years, before a child enters kindergarten or first grade. All students entering school should receive 2 doses of MMR vaccine (with the first dose administered at age 12 months or older) before enrollment. Dose 2 of MMR vaccine may be administered as soon as 4 weeks after dose 1.

The minimum interval between doses of MMRV vaccine is 3 months, although when dose 2 is administered 4 weeks following dose 1, it can be considered valid. For the first dose of measles, mumps, rubella, and varicella vaccines at age 12

Measles Vaccination Schedule

- 2-dose series at age 12 through 15 months and at age 4 through 6 years
- Minimum age for dose 1 is 12 months
- Minimum interval from dose 1 to 2 is 4 weeks for MMR and 3 months for MMRV (although a 4-week interval is valid)
- Discuss risks and benefits of MMRV versus separate MMR and VAR
  - Separate MMR and VAR vaccines preferred for dose 1 in ages 12 through 47 months
  - MMRV preferred for dose 2 and dose 1 at age 48 months or older

through 47 months, either separate MMR and varicella (VAR) vaccines, or MMRV vaccine, may be used. However, the risk of febrile seizures is about twice as high for children receiving MMRV vaccine versus separate MMR and VAR vaccines. Providers who are considering administering MMRV should discuss the benefits and risks of both vaccination options with the parents. Unless the parent or caregiver expresses a preference for MMRV, separate MMR vaccine and VAR vaccine should be administered for the first dose in this age group. For the second dose of measles, mumps, rubella, and varicella vaccines at any age and for the first dose at age 48 months or older, the use of MMRV generally is preferred over separate injections of its equivalent component vaccines (i.e., MMR vaccine and VAR vaccine).

MMR Vaccination of Adults

- Certain persons without acceptable presumptive immunity:
  - At least 1 dose MMR for unvaccinated adults
  - 2 doses MMR for students entering colleges, universities, technical and vocational schools, and other post-high-school educational institutions
  - 2 doses MMR for measles and mumps and 1 dose MMR for rubella for healthcare personnel
- Healthcare personnel during an outbreak
  - 2 doses MMR for measles or mumps outbreak and 1 dose MMR for rubella outbreak

Vaccination of Adults

Adults born in 1957 or later should receive at least 1 dose of MMR vaccine unless they have documentation of vaccination with at least 1 dose of measles, mumps, and rubella-containing vaccine or other acceptable presumptive evidence of immunity to these three diseases. Except for health care personnel who should have documented immunity, birth before 1957 generally can be considered acceptable evidence of immunity to measles, mumps, and rubella.

Colleges and other post-high-school educational institutions are potential high-risk areas for measles, mumps, and rubella transmission because of large concentrations of persons. Prematriculation vaccination requirements for measles immunity have been shown to significantly decrease the risk of measles outbreaks on college campuses where such requirements are implemented and enforced. All students entering colleges, universities, technical and vocational schools, and other institutions for post-high-school education should receive 2 doses of MMR vaccine or have other acceptable evidence of measles, mumps, and rubella immunity before entry.

For unvaccinated health care personnel born before 1957 who lack laboratory evidence of measles, mumps, or rubella immunity or laboratory confirmation of disease, health care facilities should have policies that offer 2 doses of MMR vaccine at the appropriate interval for measles and mumps and 1 dose of MMR vaccine for rubella, respectively. Health care facilities should also have policies for such personnel that recommend 2 doses of MMR vaccine during an outbreak of measles or mumps and 1 dose during an outbreak of rubella. This recommendation is based on serologic studies indicating that among hospital personnel born before 1957, 5% to 10% had no detectable measles, mumps, or rubella antibody. Adequate vaccination for health care personnel born during or after 1957 consists of 2 appropriately spaced MMR doses for measles and mumps, and at least 1 dose of MMR for rubella.

Persons who travel outside the United States are at increased risk of exposure to measles. Measles is endemic or epidemic in many countries throughout the world. Although proof of immunization is not required for entry into the United States or any other country, persons traveling or living abroad should have evidence of measles immunity. Adequate vaccination of persons who travel outside the United States is 1 dose of MMR vaccine for children age 6 through 11 months and 2 doses of an age-appropriate measles-, mumps-, and rubella-containing vaccine for children age 12 months and older and adults.

MMR Vaccination of Travelers

- Adequate vaccination for persons traveling outside the United States
  - 1 dose MMR for children age 6 through 11 months
  - 2 doses of age appropriate MMR or MMRV for children age 12 months and older and adults

Revaccination

Revaccination is recommended for certain persons. The following groups should be considered unvaccinated and should receive at least 1 dose of measles vaccine: 1) persons vaccinated before their first birthday, 2) persons vaccinated with killed measles vaccine, 3) persons vaccinated from 1963 through 1967 with an unknown type of vaccine, 4) persons who received immune globulin (IG) in addition to a further attenuated strain or vaccine of unknown type, and 5) persons with perinatal human immunodeficiency virus (HIV) infection who were vaccinated before establishment of effective antiretroviral therapy (ART) and who do not have evidence of current severe immunosuppression.

Measles-, mumps-, or rubella- virus-containing vaccine administered prior to age 12 months (e.g., for international travel) should not be counted as part of the 2-dose series. Children vaccinated before age 12 months should be revaccinated with 2 doses of appropriately spaced MMR or MMRV vaccine, the first dose administered when the child is age 12 through 15 months (12 months if the child remains in an area where disease risk is high) and the second dose at least 4 weeks later.

Persons who experienced perinatal HIV infection who may have received MMR vaccine prior to the establishment of effective combined antiretroviral therapy (cART) should be revaccinated with 2 appropriately spaced doses of MMR (i.e., the dose does not count) unless they have other acceptable current evidence of immunity. MMR series should be administered once effective cART has been established for at least 6 months and there is no evidence of severe immunosuppression.

Measles Immunity

- Born before 1957
- Serologic evidence of measles immunity (equivocal tests are considered negative)
- Laboratory confirmation of disease
- Documentation of adequate vaccination for measles

Measles Immunity

Generally, persons can be considered immune to measles if they were born before 1957, have serologic evidence of measles immunity (equivocal test results should be considered negative), or laboratory confirmation of disease, or have documentation of adequate vaccination for measles.

Measles Vaccine Efficacy

- Antibodies develop in approximately 95% of children vaccinated at age 12 months and over 99% of children who receive 2 doses
- Immunity long-term and probably lifelong in most persons

Immunogenicity and Vaccine Efficacy

Measles antibodies develop in approximately 95% of children vaccinated at age 12 months. Seroconversion rates are similar for single-antigen measles, MMR vaccine, and MMRV vaccine. Approximately 2% to 7% of children who receive only 1 dose of MMR vaccine fail to respond to it, i.e., they experience primary vaccine failure. MMR vaccine failure can occur because of passive antibody in the vaccine recipient, immaturity of the immune system, damaged vaccine, or other reasons. Most persons who fail to respond to the first dose will respond to a second dose. Studies indicate that more than 99% of persons who receive 2 doses of measles vaccine (with the first dose administered no earlier than the first birthday) develop serologic evidence of measles immunity.

Although the titer of vaccine-induced antibodies is lower than that following natural disease, both serologic and epidemiologic evidence indicate that vaccine-induced immunity appears to be long-term and probably lifelong in most persons. Most vaccinated persons who appear to lose antibody show an anamnestic immune response upon revaccination, indicating that they are probably still immune.

Although revaccination can increase antibody titer in some persons, available data indicate that the increased titer may not be sustained. Some studies indicate that waning immunity may occur after successful vaccination, but this appears to occur rarely and to play only a minor role in measles transmission and outbreaks.

Measles Vaccine Contraindications

- Contraindication
  - Severe allergic reaction to vaccine component or following a prior dose
  - Severe immunocompromise
  - Systemic high-dose corticosteroid therapy for 14 days or more
  - HIV infection, regardless of immunocompetence status*
  - Family history of congenital or heredity immunodeficiency in first-degree relatives
  - Pregnancy

*MMRV only

Contraindications and Precautions to Vaccination

As with other vaccines, a history of a severe allergic reaction (anaphylaxis) to a vaccine component or following a prior dose is a contraindication to further doses. Moderate or severe acute illness (with or without fever) in a patient is considered a precaution to vaccination, although persons with minor illness may be vaccinated.

MMR and MMRV vaccines both contain minute amounts of neomycin and gelatin. Persons with alpha-gal allergy may wish to consult their physician before receiving a vaccine that contains gelatin.

Severe immunocompromise (e.g., from hematologic and solid tumors, receipt of chemotherapy, congenital immunodeficiency, long-term immunosuppressive therapy or patients with HIV infection who are severely immunocompromised) is a contraindication for MMR and MMRV vaccination. If the person's level of immunocompetence is uncertain, the decision to vaccinate should be made by the health care provider that prescribed the immunosuppressive medication for those

patients whom immunocompromise is due to medication. Patients who have not received chemotherapy for at least 3 months, whose disease remains in remission, and who have restored immunocompetence, may receive MMR or MMRV vaccine. Healthy, susceptible close contacts of severely immunocompromised persons should be vaccinated.

Persons receiving systemic high-dose corticosteroid therapy (2 milligrams per kilogram of body weight or more per day or 20 milligrams or more per day of prednisone) for 14 days or more should not receive MMR or MMRV vaccine because of concern about vaccine safety. MMR or MMRV should not be administered for at least 1 month after cessation of systemic high-dose corticosteroid therapy. Although persons receiving high doses of systemic corticosteroids daily or on alternate days for less than 14 days generally can receive MMR or MMRV immediately after cessation of treatment, some experts prefer waiting until 2 weeks after completion of therapy.

Available data indicate that vaccination with MMR has not been associated with severe or unusual adverse reactions in HIV-infected persons who are not severely immunosuppressed, although antibody responses have been variable. MMR vaccine is recommended for susceptible HIV-infected persons age 12 months or older with no evidence of current severe immunosuppression ("no evidence of current severe immunosuppression" is defined as CD4 percentages greater than or equal to 15% for 6 months or longer for persons age 5 years or younger; and CD4 percentages greater than or equal to 15% and CD4 count greater than or equal to 200 cells/mm^3 for 6 months or longer for persons older than age 5 years). MMR vaccine is not recommended for HIV-infected persons with evidence of severe immunosuppression.

MMRV is not approved for and should not be administered to a person known to be infected with HIV.

A family history of congenital or hereditary immunodeficiency in first-degree relatives (e.g., parents and siblings) is a contraindication for MMR or MMRV vaccine, unless the immune competence of the potential vaccine recipient has been substantiated clinically or verified by a laboratory.

A history of thrombocytopenic purpura or thrombocytopenia is a precaution for MMR and MMRV vaccine. Such persons may be at increased risk for developing clinically significant thrombocytopenia after MMR or MMRV vaccination.

Simultaneous use of aspirin or aspirin-containing products is a precaution for MMRV vaccine due to the varicella component. The manufacturer recommends that vaccine recipients avoid the use of salicylates for 6 weeks after receiving MMRV vaccine because of the association between aspirin use and Reye syndrome following chickenpox.

Measles Vaccine Precautions

- Precaution
  - Moderate or severe acute illness
  - Alpha-gal allergy (consult with physician)
  - Receipt of antibody-containing blood products (wait 3 to 11 months to vaccinate)
  - History of thrombocytopenic purpura or thrombocytopenia
  - Need for tuberculin skin testing or interferon-gamma release assay testing
  - Simultaneous use of aspirin or aspirin-containing products*
  - Personal or family history of seizures of any etiology*
  - Receipt of specific antiviral drugs 24 hours before vaccination*

*MMRV only

A personal or family (i.e., sibling or parent) history of seizures of any etiology is a precaution for MMRV vaccine but not MMR. Children with a personal or family history of seizures of any etiology should ideally be vaccinated with separate MMR and VAR vaccines because the risks for using MMRV vaccine in this group of children generally outweigh the benefits.

MMR vaccine may be administered to egg-allergic persons without prior routine skin testing or the use of special protocols.

Spacing Considerations

The effect of the administration of antibody-containing blood products (e.g., immune globulin, whole blood or packed red blood cells, or intravenous immune globulin) on the response to MMR or MMRV vaccine is unknown. Because of the potential inhibition of the response to vaccination by passively transferred antibodies, neither MMR vaccine nor MMRV vaccine (nor VAR vaccine) should be administered for 3 to 11 months after receipt of antibody-containing blood products. The interval between the antibody-containing blood product and receipt of MMR or MMRV vaccine is determined by the type of product administered. Antibody-containing products should not be given for 2 weeks following vaccination unless the benefits exceed those of the vaccine. In such cases, vaccine recipients should either be revaccinated later at the appropriate intervals (ranging 3 to 11 months) or tested for immunity and revaccinated if seronegative.

Need for tuberculin skin testing or interferon-gamma release assay (IGRA) testing is a precaution for MMR and MMRV vaccine. Measles vaccine (and possibly mumps, rubella, and varicella vaccines) may transiently suppress the response to tuberculin skin test (TST) in a person infected with Mycobacterium tuberculosis. TST and measles-containing vaccine may be administered at the same visit if necessary. Simultaneously administering TST and measles-containing vaccine does not interfere with reading the TST result at 48 to 72 hours and ensures that the person has received measles vaccine. If the measles-containing vaccine has been administered recently, TST screening should be delayed for at least 4 weeks after vaccination.

Receipt of specific antiviral drugs (e.g., acyclovir, famciclovir, or valacyclovir) 24 hours before vaccination is a precaution for MMRV vaccine due to the varicella component. These drugs should be avoided for 14 days after vaccination.

Vaccination in Pregnancy

Pregnancy is a contraindication for MMR or MMRV vaccine. Pregnancy should be avoided for 4 weeks following MMR or MMRV vaccine. Close contact with a pregnant woman is not a contraindication to MMR or MMRV vaccination of the contact.

If a pregnant woman inadvertently receives MMR or MMRV vaccine, termination of pregnancy is not recommended because the risk to the fetus appears to be extremely low. Instead, individual counseling for these women is recommended.

Vaccine Safety

Studies have shown MMR and MMRV vaccines are safe and well-tolerated. The National Academy of Medicine, formerly called the Institute of Medicine, reviewed the evidence between MMR vaccination and certain adverse events. The experts determined that evidence supports a causal relation between MMR vaccination and anaphylaxis, febrile seizures, thrombocytopenic purpura, transient arthralgia, and measles inclusion body encephalitis in persons with demonstrated immunodeficiencies.

Most adverse events reported following MMR vaccination (such as fever and rash) are attributable to the measles component. After MMR vaccination, 5% to 15% of susceptible persons develop a temperature of 103°F (39.4°C) or higher, usually occurring 7 to 12 days after vaccination and generally lasting 1 or 2 days. Most persons with fever do not have other symptoms. MMR vaccine is associated with a very small risk of febrile seizures; approximately one case for every 3,000 to 4,000 doses of MMR vaccine administered. The febrile seizures typically occur 6 to 14 days after vaccination and do not appear to be associated with any long-term sequelae. Children with a personal or family history of febrile seizures or family history of epilepsy might be at increased risk for febrile seizures after MMR vaccination.

MMR vaccine may cause a transient rash in approximately 5% of vaccine recipients, usually appearing 7 to 10 days after vaccination. Laboratory testing can confirm the presence of measles or mumps vaccine virus in a recently vaccinated and potentially exposed individual.

Allergic reactions following the administration of MMR vaccine are rare. Most of these are minor and consist of a wheal and flare or urticaria at the injection site. Immediate, anaphylactic reactions to MMR vaccine occur in 1.8 to 14.4 cases per million doses.

Arthralgias and other joint symptoms are reported in up to 25% of adult women following MMR vaccination and are associated with the rubella component. Transient lymphadenopathy sometimes occurs following receipt of MMR or other rubella-containing vaccine, and parotitis has been reported rarely (less than 1%) following receipt of MMR or other mumps-containing vaccine.

Rarely, MMR vaccine may cause thrombocytopenia within two months after vaccination. The clinical course of these

Measles Vaccine Safety

MMR

- Fever of 103°F (39.4°C) or higher
  - 5%–15%
- Rash
  - 5%
- Febrile seizures
  - 1 in every 3,000 to 4,000 doses
- Anaphylactic reactions
  - 1.8 to 14.4 cases per million doses
- Arthralgias and other joint symptoms
  - 25% (adult women)

MMRV

- Fever of 102°F or higher
  - 21.5%
- Febrile seizures
  - 1 additional per 2,300 to 2,600 children age 12 through 23 months

cases is usually transient and benign, although hemorrhage occurs rarely. Based on case reports, the risk for MMR vaccine-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.

Measles inclusion body encephalitis has been documented after measles vaccination in persons with immune deficiencies. The illness is also known to occur within 1 year after initial infection with wild-type measles virus and has a high death rate. In the cases after MMR vaccination, the time from vaccination to development of measles inclusion body encephalitis was 4–9 months, consistent with development of measles inclusion body encephalitis after infection with wild-type measles virus.

In MMRV vaccine prelicensure studies conducted among children age 12 to 23 months, fever (reported as abnormal or elevated greater than or equal to 102°F oral equivalent) was observed 5 to 12 days after vaccination in 21.5% of MMRV vaccine recipients compared with 14.9% of MMR vaccine and VAR vaccine recipients. Two postlicensure studies indicated that one additional febrile seizure per 2,300 to 2,600 children age 12 through 23 months occurred 5 to 12 days after the first dose of MMRV vaccine, compared with children who had received the first dose of MMR vaccine and VAR vaccine administered as separate injections at the same visit. Data from postlicensure studies do not suggest that this increased risk exists for children age 4 to 6 years receiving the second dose of MMRV vaccine.

Multiple studies, as well as a National Academy of Medicine Vaccine Safety Review, refute a causal relationship between autism and MMR vaccine or between inflammatory bowel disease and MMR vaccine.

Vaccine Storage and Handling

For MMR-II and Proquad storage and handling specifics, refer to the manufacturer. For complete information on storage and handling best practices and recommendations, please refer to CDC's Vaccine Storage and Handling Toolkit, www.cdc.gov/vaccines/hcp/admin/storage/toolkit/storage-handling-toolkit.pdf.

Surveillance and Reporting for Measles

For information on guidance for state and local health department staff who are involved in surveillance activities for vaccine-preventable diseases, please consult the Manual for the Surveillance of Vaccine-Preventable Diseases, www.cdc.gov/vaccines/pubs/surv-manual/chapters.html.

Acknowledgements

The editors would like to acknowledge Jennifer Hamborsky and Valerie Morelli for their contributions to this chapter.

Selected References

American Academy of Pediatrics. Measles. In: Kimberlin D, Brandy M, Jackson M, et al., eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics;2018:537–50.

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

Bellini W, Rota P. Genetic diversity of wild-type measles viruses: implications for global measles elimination programs. *Emerg Infect Dis* 1998;4(1):29–35.

Bellini W, Rota J, Lowe L, et al. Subacute sclerosing panencephalitis: more cases of this fatal disease are prevented by measles immunization than was previously recognized. *J Infect Dis* 2005;192(10):1686–93.

CDC. Global measles mortality, 2000–2008. *MMWR* 2009;58(47):1321–6.

CDC. Immunization of health-care personnel. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2011;60(RR-7):1–45.

CDC. Measles, mumps, and rubella—vaccine use and strategies for elimination of measles, rubella, and congenital rubella syndrome and control of mumps: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 1998;47(No. RR-8):1–57.

CDC. Prevention of measles, rubella, congenital rubella syndrome, and mumps, 2013: summary recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2013;62(No. RR-4):1–34.

CDC. Recommendations of the Advisory Committee on Immunization Practices for use of a third dose of mumps virus-containing vaccine in persons at increased risk for mumps during an outbreak. *MMWR* 2018;67(1):33–8.

CDC. Use of combination measles, mumps, rubella, and varicella vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2010;59(No. RR-3):1–12.

Clemmons N, Wallace G, Patel M, et al. Incidence of Measles in the United States, 2001–2015. *JAMA* 2017;318(13);1279–81.

NOTES

NOTES

Patel M, Dumolard L, Nedelec Y, et al. Progress Toward Regional Measles Elimination — Worldwide, 2000-2018. *MMWR* 2019;68(48):1105–11.

France E, Glanz J, Xu S, et al. Risk of immune thrombocytopenia purpura after measles-mumps-rubella immunization in children. *Pediatrics* 2008;121(3):e687–92.

Gerber J, Offit P. Vaccines and autism: a tale of shifting hypotheses. *Clin Infect Dis* 2009;48(4):456–61.

Halsey N, Hyman S, 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);e84.

Institute of Medicine Immunization Safety Review Committee. *Institute of Medicine immunization safety review: vaccines and autism*. Washington D.C.: National Academy Press, 2004.

Parker Fiebelkorn A, Gastañaduy PA, et al. A Comparison of Postelimination Measles Epidemiology in the United States, 2009-2014 Versus 2001–2008. *J Pediatric Infect Dis Soc* 2017;6(1):40–8.

Patel M, Lee A, Redd S, et al. Increase in Measles Cases — United States, January 1–April 26, 2019. *MMWR* 2019;68(17):402–4.

Rota P, Moss W, Taketa M, et al. Measles. *Nat Rev Dis Primers* 2016;2:1–16.

Sugerman D, Barskey A, Delea M, et al. Measles outbreak in a highly vaccinated population, San Diego, 2008: role of the intentionally undervaccinated. *Pediatrics* 2010;125(4):747–55.

Vitek C, Aduddell, M, Brinton M, et al. 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(7):620–3.

Meningococcal Disease

Sarah Mbaeyi, MD; Jonathan Duffy, MD, MPH; Lucy A. McNamara, PhD

Meningococcal disease is an acute, severe illness caused by the bacterium *Neisseria meningitidis*. A leading cause of bacterial meningitis and sepsis in the United States, *N. meningitidis* can also cause pneumonia and focal disease, such as septic arthritis. As of August 2020, five meningococcal vaccines are licensed and available in the United States: three quadrivalent (serogroups A, C, W, and Y) conjugate meningococcal vaccines and two recombinant serogroup B vaccines.

Meningococcal Disease

- A leading cause of bacterial meningitis and sepsis in U.S.
- As of August 2020, five meningococcal vaccines licensed in U.S.

Neisseria meningitidis

N. meningitidis, or meningococcus, is an aerobic, gram-negative bacterium, closely related to *N. gonorrhoeae* and to several typically nonpathogenic *Neisseria* species, such as *N. lactamica*.

The outer membrane of *N. meningitidis* is surrounded by a polysaccharide capsule that is important for pathogenicity because it helps the bacterium resist phagocytosis and complement-mediated lysis. The outer membrane proteins and the capsular polysaccharide make up the main surface antigens of the organism.

Meningococci are classified into serogroups based on the structure of the polysaccharide capsule. Twelve antigenically and chemically distinct polysaccharide capsules have been described and the polysaccharide capsule determines the serogroup labeling. Almost all reported cases of invasive disease worldwide are caused by one of six serogroups: A, B, C, W, X, and Y. The relative importance of each serogroup depends on factors such as geographic location and patient age. Some strains are nongroupable and do not express capsule; these strains are most commonly associated with asymptomatic nasopharyngeal carriage rather than invasive disease.

Neisseria meningitidis

- Aerobic, gram-negative bacterium
- Outer membrane surrounded by polysaccharide capsule important for pathogenicity
- 12 antigenically and chemically distinct polysaccharide capsules that determine serogroup labeling have been described
- Almost all invasive disease caused by serogroups A, B, C, W, X, and, Y
- Relative importance of serogroups depends on factors such as geographic location and age

Pathogenesis

Meningococci are transmitted person-to-person by respiratory droplets or secretions from persons with asymptomatic colonization or meningococcal disease. The bacteria attach to and multiply in the mucosal cells of the nasopharynx and oropharynx and, in a small proportion (much less than 1%) of persons, penetrate the mucosal cells and enter the bloodstream. The bacteria can then spread through the blood to cause systemic disease and cross the blood-brain barrier into the cerebrospinal fluid (CSF) to cause meningitis.

Meningococcal Disease Pathogenesis

- Bacteria attach to and multiply in nasopharynx and oropharynx
- In <1% of persons, bacteria enter bloodstream
  - Can cause systemic disease and meningitis

Meningococcal Disease Clinical Features

- Incubation period 3 to 4 days (range, 1 to 10 days)
- Meningitis is the most common presentation of invasive disease (~50% of U.S. cases)
  - Sudden onset of fever, headache, stiff neck, nausea, vomiting, photophobia, altered mental status
- Meningococcal septicemia (30% of cases)
  - Abrupt onset of fever, chills, cold hands and feet, severe aches or pain, vomiting, diarrhea, rash
- Bacteremic pneumonia (15% of cases)
- Meningococci occasionally cause noninvasive infections
- Risk factors for invasive disease
  - Persistent complement component deficiencies
  - Functional or anatomic asplenia
  - HIV infection
  - Travel to or residence in a country where disease is hyperendemic or epidemic
  - Exposure during an outbreak
  - Microbiologists who routinely work with isolates of *N. meningitidis*
  - Household crowding
  - Smoking
  - Antecedent viral upper respiratory infection

Clinical Features

The incubation period of meningococcal disease is typically 3 to 4 days, with a range of 1 to 10 days. Meningitis is the most common presentation of invasive meningococcal disease and is found in about 50% of cases in the United States. Symptoms are similar to those seen in other forms of bacterial meningitis, and typically include 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 septicemia (bloodstream infection or meningococcemia) occurs without meningitis in about 30% of invasive meningococcal infections. This condition is characterized by abrupt onset of fever; chills; cold hands and feet; severe aches or pain in the muscles, joints, chest, or abdomen; vomiting; diarrhea; and a petechial or purpuric rash often associated with hypotension, shock, acute adrenal hemorrhage, and multiorgan failure. An additional 15% of U.S. cases present with bacteremic pneumonia; this is the most common presentation in adults over 65 years of age. Other syndromes involving isolation of meningococci from normally sterile body sites, such as septic arthritis, can also occur.

Meningococci also occasionally cause noninvasive infections such as conjunctivitis or urethritis. Noninvasive illness due to meningococci is not nationally notifiable and the incidence is unclear. Throughout this chapter, risk factors and demographics described apply only to invasive, reportable meningococcal disease cases and the term *meningococcal disease* refers to *invasive meningococcal disease*. The overall case-fatality ratio of meningococcal disease is 10% to 15%, even with appropriate antibiotic therapy, and can be higher in persons with meningococcemia. As many as 20% of survivors have permanent sequelae, such as hearing loss, neurologic damage, or loss of a limb.

In the United States, incidence of meningococcal disease is highest among infants younger than age 1 year, followed by children age 1 through 4 years. A second peak of disease incidence is found in young adults 17 through 21 years of age. Incidence increases again in adults older than 85 years of age.

Risk factors for the development of meningococcal disease include persistent complement component deficiencies (including use of a complement component inhibitor, eculizumab [Soliris®] or ravulizumab-cwvz [Ultomiris]), functional or anatomic asplenia, HIV infection, travel to or residence in a country where meningococcal disease is hyperendemic or epidemic, and exposure during an outbreak of meningococcal disease. Microbiologists who routinely work with isolates of *N. meningitidis* are also at risk. In

addition, household crowding, active and passive smoking, and antecedent viral upper respiratory infection have been associated with meningococcal disease transmission.

Laboratory Testing

Meningococcal disease is diagnosed by culture of *N. meningitidis* from a normally sterile site (e.g., blood, CSF) or purpuric lesions. Meningococcal disease may also be diagnosed through detection of *N. meningitidis*-specific nucleic acid in a specimen obtained from a normally sterile site using a validated polymerase chain reaction (PCR) assay. Although culture remains the gold standard for diagnosis of meningococcal disease, PCR is useful for detection of *N. meningitidis* from clinical samples, particularly when a patient was treated with antibiotics prior to specimen collection. Identification of gram-negative diplococci identified in a sterile site specimen strongly suggests *N. meningitidis* but is not confirmatory.

Once the diagnosis of meningococcal disease has been confirmed, the serogroup should be identified through slide agglutination or real-time PCR. Laboratories that cannot perform serogrouping should transfer the isolate or specimen to a reference laboratory, such as their state public health laboratory. Several new commercial multiplex PCR assays capable of simultaneously testing a single specimen for an array of pathogens have become available (e.g., FilmArray® Blood Culture Identification Panel and FilmArray® Meningitis/Encephalitis Panel by PCR from ARUP Laboratories). While these assays can rapidly identify *N. meningitidis* species, most do not determine serogroup. Thus, laboratories should continue to perform simultaneous culture and use validated, specific, real-time PCR assays capable of detecting and differentiating meningococcal serogroups. Otherwise, additional steps need to be taken, including performing a reflex culture or, at a minimum, retaining a clinical specimen for further testing at a public health laboratory.

Molecular typing using whole genome sequencing (WGS) can provide useful epidemiologic information, particularly if an outbreak of meningococcal disease is suspected.

Serologic testing (e.g., enzyme immunoassay) for antibodies to meningococcal antigens is not validated for clinical use in the United States. Serologic testing should not be used to establish the diagnosis of meningococcal disease or to determine whether a patient should receive a meningococcal vaccination.

Medical Management

Empiric therapy with broad-spectrum antibiotics (including a third-generation cephalosporin) should be started promptly when meningococcal disease is suspected, ideally after appropriate cultures are obtained.

Once *N. meningitidis* infection has been confirmed, treatment may be continued with penicillin, ampicillin, cefotaxime, or ceftriaxone. However, because there have been recent reports of penicillin-resistant, β-lactamase-producing *N. meningitidis* serogroup Y cases in the United States, healthcare providers should ascertain susceptibility of meningococcal isolates to penicillin before using penicillin or ampicillin for treatment.

Antimicrobial Chemoprophylaxis

Antimicrobial Chemoprophylaxis

- Primary means for prevention of sporadic meningococcal disease
- Close contacts of infected persons: Household members, childcare center contacts, anyone directly exposed to patient's oral secretions during the 7 days before symptom onset
- Administer as soon as possible, ideally less than 24 hours after identification of index patient

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, childcare 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) during the 7 days before symptom onset. Healthcare personnel should receive chemoprophylaxis if they were managing an airway or were exposed to respiratory secretions of a patient with meningococcal disease.

For travelers, antimicrobial chemoprophylaxis should be considered for any passenger who had direct contact with respiratory secretions from an index patient or for anyone seated directly next to an index patient on a prolonged flight (i.e., one lasting more than 8 hours), or within one seat in any direction on a flight of any duration if the index patient was coughing or vomiting on the flight. Any case of meningococcal disease in a person who has recently traveled should be reported to the local quarantine station to determine whether an air travel contact investigation is indicated.

Chemoprophylaxis is not recommended for close contacts of patients with evidence of *N. meningitidis* only in nonsterile sites (e.g., oropharyngeal, endotracheal, conjunctival). Reports of secondary cases after close contact with persons with noninvasive pneumonia or conjunctivitis are rare; there is no evidence of substantive excess risk. Furthermore, there is no indication to treat persons who are asymptomatic nasopharyngeal carriers.

Because the rate of secondary disease for close contacts is highest immediately after onset of disease in the index patient, antimicrobial chemoprophylaxis should be administered as soon as possible, ideally less than 24 hours after identification of the index patient. Conversely, chemoprophylaxis administered

more than 14 days after onset of illness in the index patient is probably of limited or no value. Oropharyngeal or nasopharyngeal cultures are not helpful in determining the need for chemoprophylaxis and might unnecessarily delay institution of this preventive measure.

Rifampin, ciprofloxacin, and ceftriaxone are 90% to 95% effective in reducing nasopharyngeal carriage of *N. meningitidis* and are all acceptable antimicrobial agents for chemoprophylaxis. Because there have been recent reports of ciprofloxacin-resistant, β-lactamase-producing *N. meningitidis* serogroup Y cases in the United States, clinicians and public health staff should consider obtaining antimicrobial susceptibility testing of meningococcal isolates to inform prophylaxis decisions if their state has reported a case of meningococcal disease caused by ciprofloxacin-resistant strains within the past 2 years. Clinicians should report suspected chemoprophylaxis failures to their public health departments. Systemic antimicrobial therapy for meningococcal disease with agents other than ceftriaxone or other third-generation cephalosporins might not reliably eradicate nasopharyngeal carriage of *N. meningitidis*. If other agents have been used for treatment, the patient should receive chemoprophylactic antibiotics for eradication of nasopharyngeal carriage before being discharged from the hospital.

Epidemiology

Occurrence

Meningococcal disease occurs worldwide. Incidence rates vary by serogroup and geography.

Reservoir

Humans are the only natural reservoir of meningococcus. At any given time, about 10% of adolescents and adults are asymptomatic nasopharyngeal carriers of *N. meningitidis*. Many of these carried strains are nongroupable (not encapsulated) and unlikely to cause disease in most people.

Transmission

Primary mode is by respiratory droplet spread or by direct contact with respiratory secretions.

Temporal Pattern

Meningococcal disease occurs throughout the year; however, the incidence is highest in the late winter and early spring.

Meningococcal Disease Epidemiology

- Reservoir
  - Human
- Transmission
  - Respiratory droplets or direct contact with respiratory secretions
- Temporal pattern
  - Peaks in late winter and early spring
- Communicability
  - Generally limited

Communicability

The communicability of *N. meningitidis* is generally limited. In studies of households in which a case of meningococcal disease has occurred, only 3% to 4% of households had secondary cases. Most households had only one secondary case. Estimates of the risk of secondary transmission are generally 2–4 cases per 1,000 household members at risk. However, this risk is 500 to 800 times greater than in the general population.

Meningococcal Disease Secular Trends in the United States

- In 2018, 329 total cases reported (0.10 per 100,000 population)
- Serogroups B and C major causes of meningococcal disease
- Proportion of cases caused by each serogroup varies by age group
- Outbreaks account for 5% of reported cases

Secular Trends in the United States

Incidence of meningococcal disease in the United States has declined annually following a peak in the late 1990s. In 2018, 329 total cases were reported in the United States, representing an incidence of 0.10 per 100,000 population. Serogroups B and C are the major causes of meningococcal disease in the United States, each being responsible for approximately 25% to 40% of cases; serogroups W and Y, along with nongroupable meningococci, are each responsible for another 5% to 15%. The proportion of cases caused by each serogroup varies by age group. Approximately 60% of disease among children and young adults under 24 years of age is caused by serogroup B. In particular, among individuals 18 to 24 years of age, college students have more than three times the risk of serogroup B meningococcal disease as similarly aged people not attending college. Meanwhile, serogroups C, W, or Y cause about 60% of all cases of meningococcal disease among persons 24 years of age and older.

In the United States, meningococcal outbreaks account for about 5% of reported cases (i.e., 95% of cases are sporadic). An outbreak is defined as 2–3 outbreak-associated cases (e.g., cases of the same serogroup unless found to be genetically unrelated by molecular typing methods) in an organization (e.g., school, college, correctional facility) during a three-month period, or multiple outbreak-associated cases with an incidence of meningococcal disease that is above the expected incidence in a community during a three-month period. During 2010 through 2018, multiple serogroup B outbreaks among university students and serogroup C outbreaks among men who have sex with men were reported. Other communities and organizations, including populations experiencing homelessness and correctional facilities, also experienced outbreaks during this time.

Meningococcal Vaccines

Characteristics

Meningococcal Polysaccharide Vaccine

As of 2017, meningococcal polysaccharide vaccine (Menomune) is no longer available in the United States.

Quadrivalent Meningococcal Conjugate (Serogroups A, C, W, Y) Vaccines

Three quadrivalent meningococcal conjugate vaccines are licensed for use in the United States: MenACWY-D (Menactra), MenACWY-CRM (Menveo), and MenACWY-TT (MenQuadfi). The combination Hib and bivalent meningococcal conjugate vaccine, Hib-MenCY (MenHibrix), is no longer available in the United States.

Menactra is approved for use in persons age 9 months through 55 years, Menveo is approved for use in persons age 2 months through 55 years, and MenQuadfi is approved for use in persons age 2 years or older. Menveo is prepared using media containing yeast extracts. Quadrivalent meningococcal conjugate vaccines are administered by intramuscular injection and do not contain an adjuvant, antibiotic, or preservative, although formaldehyde is added during the manufacturing process.

Serogroup B Meningococcal Vaccines

Two recombinant serogroup B meningococcal (MenB) vaccines are licensed for use in the United States: MenB-FHbp (Trumenba) and MenB-4C (Bexsero).

Trumenba and Bexsero are approved for use in persons age 10 through 25 years and are administered by intramuscular injection. Each dose of Trumenba and Bexsero contain aluminum as an adjuvant. Bexsero contains kanamycin as an antibiotic. Neither Trumenba nor Bexsero contain a preservative. The tip caps of prefilled syringes of Bexsero contain latex.

Meningococcal Vaccines

- Quadrivalent Meningococcal Conjugate Vaccines
  - MenACWY-D (Menactra)
  - MenACWY-CRM (Menevo)
  - MenACWY-TT (MenQuadfi)
- Serogroup B Meningococcal Vaccines
  - MenB-FHbp (Trumenba)
  - MenB-4C (Bexsero)

Meningococcal Vaccine Characteristics

- Quadrivalent Meningococcal Conjugate Vaccines
  - Administered by intramuscular injection
  - Do not contain an adjuvant, antibiotic, or preservative
- Serogroup B Meningococcal Vaccines
  - Administered by intramuscular injection
  - Contain aluminum as an adjuvant
  - MenB-4C (Bexsero) contains kanamycin as an antibiotic and its prefilled syringes contain latex

Vaccination Schedule And Use

Meningococcal Conjugate Vaccines

The Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination with MenACWY vaccine for all adolescents at age 11 through 18 years, with the first dose at age 11 or 12 years and a booster dose at age 16 years. For adolescents who receive the first dose at age 13 through 15 years, a one-time booster dose should be administered, preferably at age 16 through 18 years. Healthy persons who receive their first routine dose of MenACWY vaccine at or after age 16 years do not need a booster dose unless they become at

Meningococcal Vaccination Schedule

- Quadrivalent Meningococcal Conjugate Vaccines
  - 1 dose at age 11 or 12 years
  - Booster dose at age 16 years
  - Healthy persons who receive first dose at or after age 16 years do not need a booster dose unless they become at increased risk for meningococcal disease
  - Schedule for persons at increased risk for meningococcal disease varies by risk group and age (see tables)
- Serogroup B Meningococcal Vaccines
  - Recommended for persons age 10 years or older who are at increased risk of serogroup B meningococcal disease (see tables)
    - 2-dose series of Bexsero at 0 and 1 month or
    - 3-dose series of Trumenba at 0, 1–2, and 6 months
  - Shared clinical decision making for adolescents age 16 through 23 years

increased risk for meningococcal disease. Routine vaccination of healthy persons who are not at increased risk for meningococcal disease is not recommended after age 21 years.

ACIP also recommends vaccination for persons age 2 months or older at increased risk for meningococcal disease due to serogroups A, C, W, or Y. This recommendation includes:

- Persons with persistent complement component deficiencies, including persons taking eculizumab or ravulizumab-cwvz
- Persons who have functional or anatomic asplenia, including sickle cell disease
- Persons with HIV infection
- Microbiologists who are routinely exposed to isolates of *N. meningitidis*
- Persons identified by public health officials to be at increased risk during a meningococcal disease outbreak due to serogroup A, C, W, or Y
- Persons who travel to or reside in countries where meningococcal disease is endemic or hyperendemic, including the "meningitis belt" of sub-Saharan Africa or the Kingdom of Saudi Arabia during the annual Hajj and Umrah pilgrimages

Infants and children who received Hib-MenCY and are traveling to areas with high endemic rates of meningococcal disease are not protected against serogroups A and W and should receive age-appropriate MenACWY vaccine.

MenQuadfi, but not Menactra or Menveo, is licensed for use in adults age 56 years or older. However, any of these vaccines can be used to vaccinate people in this age group who are recommended to receive quadrivalent meningococcal vaccine because of increased risk for meningococcal disease.

In children at increased risk for meningococcal disease, Menactra should be given either before or at the same time as DTaP to avoid interference with the immune response to meningococcal vaccine. In addition, because of the high risk for invasive pneumococcal disease, children with functional or anatomic asplenia or HIV infection should not be vaccinated with Menactra before age 2 years to avoid interference with the immune response to pneumococcal conjugate vaccine (PCV13). If Menactra is used in persons of any age with asplenia or HIV, it should not be administered until at least 4 weeks after completion of all PCV13 doses. There are no similar constraints on Menveo or MenQuadfi administration. Booster vaccination is recommended for persons who remain at increased risk of meningococcal disease. If the most recent dose was received at younger than 7 years, a booster dose should be given after

3 years. If the most recent dose was received at age 7 years or older, a booster dose should be administered after 5 years and every 5 years thereafter as long as the person remains at increased risk for meningococcal disease.

Menactra, Menveo, or MenQuadfi can be administered at the same visit as other indicated vaccines with one exception. In persons with anatomic or functional asplenia and/or HIV infection, Menactra and pneumococcal conjugate vaccine (PCV13) should not be administered simultaneously.

If the liquid C-W-Y component of Menveo is administered alone (without using it to reconstitute the lyophilized A component), revaccination may not be needed. Serogroup A disease is rare in the United States, so revaccination is not necessary if the person does not plan to travel outside the United States. However, the person should be revaccinated with a properly reconstituted dose of Menveo, or a dose of Menactra or MenQuadfi if they are traveling internationally, especially if traveling to Africa. There is no minimum interval between the incomplete dose given in error and the repeat dose.

Serogroup B Meningococcal Vaccines

ACIP recommends MenB vaccine for persons 10 years of age or older who are at increased risk of serogroup B meningococcal disease. This recommendation includes persons with persistent complement component deficiencies, including persons taking eculizumab or ravulizumab; persons who have anatomic or functional asplenia, including sickle cell disease; microbiologists who are routinely exposed to isolates of *N. meningitidis*; or anyone identified by public health officials to be at increased risk because of a serogroup B meningococcal disease outbreak. In persons at increased risk for serogroup B meningococcal disease, ACIP recommends either a 2-dose series of Bexsero at 0 and 1 month (or longer), or a 3-dose series of Trumenba at 0, 1 to 2, and 6 months. See the tables on pages 241-242 for details on ACIP MenB vaccine recommendations for persons at increased risk for meningococcal disease. If the second dose of Bexsero or Trumenba dose is given earlier than the recommended interval, then the dose should be repeated at least 4 weeks after the last dose. However, if the second dose of Trumenba is administered at an interval of 6 months or more, a third dose does not need to be administered. If the third dose of Trumenba is administered earlier than 4 months after the second dose, the dose should be repeated at least 4 months after the last dose.

ACIP also recommends adolescents age 16 through 23 years receive MenB vaccine for short-term protection against most strains of serogroup B meningococcal disease based on shared clinical decision-making. The preferred age for vaccination is 16 through 18 years. In healthy adolescents, either a 2-dose series of Bexsero at 0 and 1 month (or longer) or a 2-dose series of

Trumenba at 0 and 6 months may be used. If the second dose of Bexsero is given earlier than the recommended interval, the dose should be repeated at least 4 weeks after the last dose. If the second dose of Trumenba is administered earlier than 6 months after the first dose, a third dose should be administered at least 4 months after the second dose.

Persons who have completed a MenB primary series and who become or remain at increased risk for meningococcal disease are recommended to receive booster vaccination. For persons 10 years of age or older with complement deficiency, complement inhibitor use, asplenia, or who are microbiologists routinely exposed to isolates, ACIP recommends a booster dose one year following completion of a MenB primary series followed by booster doses every 2 to 3 years thereafter, for as long as increased risk remains. For persons 10 years of age or older determined by public health officials to be at increased risk during a serogroup B outbreak, ACIP recommends a one-time booster dose if it has been at least one year since completion of the primary series. (A booster interval of at least six months may be considered by public health officials depending on the specific outbreak, vaccination strategy, and projected duration of elevated risk). Serogroup B meningococcal vaccine may be administered simultaneously or at any interval with other live or inactivated vaccines, including meningococcal conjugate vaccines.

Trumenba and Bexsero are not interchangeable. The same serogroup B meningococcal vaccine brand must be used for all doses of the series. If doses of both brands have been

administered to the same patient, the provider should ensure that the patient receives a complete series of either brand and ignore any doses of the other brand. The next dose of the selected brand should be given no sooner than the recommended interval after the previous dose of the same brand AND at least 4 weeks after the last (or only) dose of the other brand.

ACIP meningococcal vaccine recommendations for persons at increased risk for meningococcal disease (age 2 through 23 months)

Age	Risk Group	MenACWY primary series	MenACWY booster dose	MenB vaccine recommendation*	MenB booster dose*
2–23 months	• Asplenia • HIV infection	Menactra: Not recommended MenQuadfi: Not recommended Menveo: • 1st dose at 8 weeks: 4-dose series at 2, 4, 6, and 12 months • 1st dose at 7–23 months: 2 doses at least 12 weeks apart, with 2nd dose at age 1 year or older	Recommended for individuals at continued risk.†	No recommendation	No recommendation
	• Complement deficiency • Outbreak • Travel	MenQuadfi: Not recommended Menactra: • 9–23 months: 2 doses at least 12 weeks apart *or* Menveo: • 1st dose at 8 weeks: 4-dose series at 2, 4, 6, and 12 months • 1st dose at 7–23 months: 2 doses at least 12 weeks apart, with 2nd dose at age 1 year or older	Recommended for individuals at continued risk.†	No recommendation	No recommendation

*Note that MenB-FHbp and MenB-4C are not interchangeable; the same vaccine should be used for all doses, including booster doses.

†Revaccination with meningococcal conjugate vaccine is recommended after 3 years for children who received their last dose at <7 years of age. Revaccination is recommended after 5 years for people who received their last dose at ≥7 years of age, and every 5 years thereafter for people at continued risk.

ACIP meningococcal vaccine recommendations for persons at increased risk for meningococcal disease (age 2 through 9 years)

Age	Risk Group	MenACWY primary series	MenACWY booster dose	MenB vaccine recommendation*	MenB booster dose*
2–9 years	• Asplenia[†] • HIV infection[†] • Complement deficiency	2 doses at least 8 weeks apart	Recommended for individuals at continued risk.[§]	No recommendation	No recommendation
	• Outbreak • Travel	1 dose	Recommended for individuals at continued risk.[§]	No recommendation	No recommendation

*Note that MenB-FHbp and MenB-4C are not interchangeable; the same vaccine should be used for all doses, including booster doses.

[†]Menactra must be administered at least 4 weeks after completion of PCV13 series.

[§]Revaccination with meningococcal conjugate vaccine is recommended after 3 years for children who received their last dose at <7 years of age. Revaccination is recommended after 5 years for people who received their last dose at ≥7 years of age, and every 5 years thereafter for people at continued risk.

ACIP meningococcal vaccine recommendations for persons at increased risk for meningococcal disease (age 10 years or older)

Age	Risk Group	MenACWY primary series	MenACWY booster dose	MenB vaccine recommendation*	MenB booster dose*
≥10 years	• Asplenia[†] • Complement deficiency	2 doses at least 8 weeks apart	Recommended for individuals at continued risk.[§]	Trumenba: 3-dose series at 0, 1–2, and 6 months or Bexsero: 2-dose series at least 1 month apart	For individuals who remain at increased risk of serogroup B disease, a single dose of MenB vaccine is recommended 1 year after completion of the primary vaccination series and every 2-3 years thereafter
	HIV infection[†]	2 doses at least 8 weeks apart	Recommended for individuals at continued risk.[§]	No recommendation	No recommendation
	Microbiologist	1 dose	Recommended for individuals at continued risk.[§]	Trumenba: 3-dose series at 0, 1–2, and 6 months or Bexsero: 2-dose series at least 1 month apart	For individuals who remain at increased risk of serogroup B disease, a single dose of MenB vaccine is recommended 1 year after completion of the primary vaccination series and every 2-3 years thereafter
	Outbreak	1 dose	Recommended for individuals at continued risk.[§]	Trumenba: 3-dose series at 0, 1–2, and 6 months or Bexsero: 2-dose series at least 1 month apart	For individuals who were previously vaccinated and identified as being at increased risk during an outbreak, a single dose of MenB vaccine is recommended if it has been ≥1 year since MenB primary series completion (≥6 month interval might also be considered by public health professionals).
	Travel	1 dose	Recommended for individuals at continued risk.[§]	No recommendation	No recommendation

*Note that MenB-FHbp and MenB-4C are not interchangeable; the same vaccine should be used for all doses, including booster doses.

[†]Menactra must be administered at least 4 weeks after completion of PCV13 series.

[§]Revaccination with meningococcal conjugate vaccine is recommended after 3 years for children who received their last dose at <7 years of age. Revaccination is recommended after 5 years for people who received their last dose at ≥7 years of age, and every 5 years thereafter for people at continued risk.

Immunogenicity and Vaccine Effectiveness

Meningococcal Conjugate Vaccines

In clinical trials, the immunogenicity of MenACWY vaccines was assessed as seroconversion rates, defined as achieving a seroresponse at a predefined serum bactericidal antibody level for each serogroup, or the proportion of participants with a fourfold or greater increase in bactericidal antibody to each serogroup. An evaluation of MenACWY-D effectiveness (VE) in U.S. adolescents demonstrated that the overall effectiveness is 69% (51 to 80%). Effectiveness was 77% (57 to 88%) for serogroup C and 51% (1 to 76%) for serogroup Y. Effectiveness waned over time; VE was 79% (49 to 91%) within 1 year of vaccination, 69% (44 to 83%) 1 to 2 years after vaccination, and 61% (25 to 79%) 3 to 8 years after vaccination. These results, along with antibody persistence data showing waning immunity 3 to 5 years following a single dose, informed the ACIP recommendation for a booster dose in adolescents at age 16 years following a primary dose at age 11 or 12 years.

Serogroup B Meningococcal Vaccines

For both Trumenba and Bexsero, antibody responses were measured by serum bactericidal activity using human complement against selected meningococcal serogroup B strains. Immunogenicity was assessed as the proportion of subjects who achieved a fourfold or greater increase in serum bactericidal activity using human complement (hSBA) titer for each of the serogroup B strains tested, and the proportion of subjects who achieved a titer greater than or equal to the lower limit of quantification of the assay for all strains (composite response).

In a multicenter study conducted among adolescents age 11 to 17 years in the United States, 81% of subjects who received Trumenba and concomitant quadrivalent HPV vaccine (4vHPV) had a composite response, and 84% of subjects who received Trumenba with saline had a composite response.

In a randomized, controlled trial in the United Kingdom among college students age 18 to 24 years, 88% of recipients of both doses of Bexsero had a composite response at one month following the second dose. At 11 months after the second dose, 66% of recipients had a composite response. In a randomized, controlled trial in Australia and Canada among adolescents age 11 to 17 years, 63% of recipients had a composite response one month after the second dose.

Meningococcal Vaccine Efficacy

- Quadrivalent Meningococcal Conjugate Vaccines
  - 69% effective in U.S. adolescents
  - Effectiveness wanes over time
- Serogroup B Meningococcal Vaccines
  - Multicenter study demonstrated 84% of adolescents receiving Trumenba with saline had composite response
  - In a randomized, controlled trial 88% of college students receiving 2 doses of Bexsero had a composite response after 1 month; 66% at 11 months

Meningococcal Vaccines Contraindications and Precaution

- Contraindication
  - Severe allergic reaction to vaccine component or following prior dose
  - Severe allergic reaction after any of the following*:
    - A previous dose of Menactra, Menveo, or MenQuadfi
    - Any component of Menactra, Menveo, or MenQuadfi vaccines
    - Any other meningococcal, diphtheria toxoid-, tetanus toxoid-, or CRM_{197}-containing vaccine
- Precaution
  - Moderate or severe acute illness
  - Latex sensitivity (Bexsero only)

*Contraindication for MenACWY vaccines

Meningococcal Vaccine Safety

- Quadrivalent Meningococcal Conjugate Vaccines
  - Injection site pain, erythema
  - Irritability, drowsiness, myalgia, headache, fatigue, sleepiness, malaise
- Serogroup B Meningococcal Vaccines
  - Injection site pain, induration, erythema, swelling
  - Headache, fatigue, myalgia, arthralgia

Contraindications and Precautions to Vaccination

As with other vaccines, a history of a severe allergic reaction (anaphylaxis) to a vaccine component or following a prior dose is a contraindication to further doses. Moderate or severe acute illness (with or without fever) in a patient is considered a precaution to vaccination, although persons with minor illness may be vaccinated.

Vaccination with MenACWY vaccine is contraindicated for persons who have had a severe allergic reaction (e.g., anaphylaxis) after any the following:

- A previous dose of Menactra, Menveo, or MenQuadfi
- Any component of Menactra, Menveo, or MenQuadfi vaccines
- Any other meningococcal, diphtheria toxoid-, tetanus toxoid-, or CRM_{197}-containing vaccine.

After reviewing safety studies, ACIP voted in 2010 to remove a history of Guillain-Barré syndrome (GBS) as a precaution for vaccination with any MenACWY vaccine including Menactra. However, a history of GBS continues to be listed as a precaution in the package insert for Menactra.

For both Bexsero and Trumenba, severe allergic reaction (e.g., anaphylaxis) after a previous dose or to any vaccine component is a contraindication for vaccination. Latex sensitivity is listed as a precaution for Bexsero because the tip caps of the prefilled syringes contain natural rubber latex. Menveo is prepared using media containing yeast extracts.

Vaccination during Pregnancy

To date, no randomized clinical trials have been conducted to evaluate use of MenACWY or MenB vaccines in pregnant or lactating women. MenACWY vaccines are recommended for lactating women if otherwise indicated. ACIP recommends that Bexsero or Trumenba vaccination of pregnant women should be deferred unless the woman is at increased risk and, after consultation with her health care provider, the benefits of vaccination are considered to outweigh the potential risks.

Vaccine Safety

Meningococcal Conjugate Vaccines

In clinical trials of Menactra, the most common injection-site reactions were pain (31% to 69%) and erythema (3% to 43%). The most common systemic reactions in infants and children were irritability and drowsiness; in adolescents and adults the most common were myalgia, headache, and fatigue. Most symptoms were mild-to-moderate and resolved within three

days. The Vaccine Adverse Event Reporting System (VAERS) received 13,075 reports for Menactra from 2005 through June 2016, during which time over 70 million Menactra doses were distributed. The most commonly reported adverse events were injection site erythema, fever, and headache. Reported adverse events were consistent with the findings from pre-licensure studies, and no new safety concerns were identified. A cohort study in which 1.4 million doses of Menactra were administered found that Menactra vaccination was associated with a small risk of syncope and medically-attended fever but identified no new safety concerns.

In clinical trials of Menveo, the most common injection-site reactions were pain (8% to 54%) and erythema (12% to 39%). The most common systemic reactions in infants and toddlers were irritability and sleepiness. The most common in children were irritability, myalgia, headache, and sleepiness. In adolescents and adults, myalgia, headache, and fatigue were the most common. Most symptoms were mild-to-moderate and resolved within three days. VAERS received 2,614 reports for Menveo from 2010 through 2015, during which time 8.2 million Menveo doses were distributed. The most commonly reported adverse events were consistent with the findings from pre-licensure studies, and no new safety concerns were identified. In a postlicensure cohort study in which approximately 49,000 individuals aged 11 to 21 years received Menveo, an increased risk of Bell's palsy during the 84 days following vaccination was observed when Menveo was administered simultaneously with other vaccines but not when Menveo was administered alone. However, this finding was based on only eight patients, several of whom had other conditions or infections that might precede Bell's palsy. The importance of this finding is uncertain.

In clinical trials of MenQuadfi, the most common injection-site reaction after the primary dose in all age groups was pain (26% to 45%). The most common systemic reactions were myalgia, headache, and malaise. Solicited adverse reactions following a booster dose in adolescents and adults were comparable to those observed following primary vaccination. MenQuadfi was not yet in use at the time of this publication and postlicensure vaccine safety evaluations will be performed.

Serogroup B Meningococcal Vaccines

In clinical trials of Trumenba, the most common local reactions were injection site pain (72% to 93%), induration (21% to 37%), and erythema (10% to 24%). The most common systemic reactions were headache (27% to 67%), fatigue (30% to 66%), myalgia (21% to 40%), and arthralgia (11% to 33%). Most symptoms were mild-to-moderate and resolved within five days. VAERS received 1,719 reports for Trumenba from 2014 through June 2018. The most commonly reported adverse events were fever, headache, and injection site pain. Reported adverse

events were consistent with the findings from pre-licensure studies, and no new safety concerns were identified. Adverse events following Trumenba were also evaluated during a mass vaccination campaign on a university campus in which over 10,000 doses were administered; rates of injection site pain, fatigue, myalgia, fevers, and chills were similar to those reported during clinical trials.

In clinical trials of Bexsero, the most common local reactions were injection site pain (82% to 98%), erythema (35% to 68%), swelling (26% to 47%), and induration (10% to 48%). The most common systemic reactions were headache (21% to 65%), fatigue (18% to 73%), myalgia (17% to 75%), and arthralgia (8% to 42%). VAERS received 1,470 reports for Bexsero from 2015 through June 2018. The most commonly reported adverse events were injection site pain, fever, and headache; transient decreased mobility of the arm where Bexsero was injected was also disproportionately reported. Otherwise, reported adverse events were consistent with the findings from pre-licensure studies, and no new safety concerns were identified. Adverse events following Bexsero were also evaluated during several mass vaccination campaigns in the United States and Canada. The most commonly reported adverse events were consistent with findings based on clinical trial data (e.g., fever, injection site pain, arm pain), and 0.88 syncopal events per 1,000 persons were observed in the U.S. evaluation.

Vaccine Storage and Handling

MMenACWY (Menactra, Menveo and MenQuadfi) and MenB (Bexsero and Trumenba) should be maintained at refrigerator temperature between 2°C and 8°C (36°F and 46°F). Whenever possible, the lyophilized and liquid components of Menveo should be stored together.

The MenA (lyophilized) component of Menveo should only be reconstituted using the liquid C-W-Y component of Menveo. No other vaccine or diluent can be used for this purpose. The reconstituted vaccine should be used immediately but may be held at or below 25°C (77°F) for up to 8 hours.

Manufacturer package inserts contain additional information. For complete information on storage and handling best practices and recommendations, please refer to CDC's Vaccine Storage and Handling Toolkit, https://www.cdc.gov/vaccines/hcp/admin/storage/toolkit/storage-handling-toolkit.pdf.

Surveillance and Reporting of Meningococcal Disease

Meningococcal disease is a reportable condition in all states. Healthcare personnel should immediately report any case of invasive meningococcal disease to local and state health departments. This is essential so that antimicrobial chemoprophylaxis can be rapidly administered to close contacts of the case. For guidance for state and local health department staff who are involved in surveillance activities for vaccine-preventable diseases, please consult the Manual for the Surveillance of Vaccine-Preventable Diseases, https://www.cdc.gov/vaccines/pubs/surv-manual/chapters.html.

Acknowledgements

The editors wish to acknowledge Jennifer Hamborsky, Susan Hariri, and Andrew Kroger for their contributions to this chapter.

NOTES

NOTES

Selected References

CDC. Guidance for the Evaluation and Public Health Management of Suspected Outbreaks of Meningococcal Disease. Version 2.0. 2019. https://www.cdc.gov/meningococcal/downloads/meningococcal-outbreak-guidance.pdf. Accessed September 1, 2020.

CDC. Meningococcal Disease – Surveillance. https://www.cdc.gov/meningococcal/surveillance/index.html. Accessed September 13, 2020.

CDC. Meningococcal Vaccination: Recommendations of the Advisory Committee on Immunization Practices, United States, 2020. *MMWR* 2020;69(9):1–41.

CDC. Recommendations for Use of Meningococcal Conjugtae Vaccines in HIV-Infected Persons—Advisory Committee on Immunization Practices, 2016. *MMWR* Morb Mortal Wkly Rep 2016;65(43):1189-94.

CDC. Updated Recommendations for Use of MenB-FHbp Serogroup B Meningococcal Vaccine—Advisory Committee on Immunization Practices, 2016. *MMWR Morb Mortal Wkly Rep* 2017;66(19):509-13.

CDC. Use of Serogroup B Meningococcal Vaccines in Adolescents and Young Adults: Recommendations of the Advisory Committee on Immunization Practices, 2015. *MMWR Morb Mortal Wkly Rep* 2015;64:1171–6.

CDC. Use of Serogroup B Meningococcal Vaccines in Persons Aged ≥10 Years at Increased Risk for Serogroup B Meningococcal Disease: Recommendations of the Advisory Committee on Immunization Practices, 2015. *MMWR Morb Mortal Wkly Rep* 2015;64(22):608–12.

Harrison L, Granoff D, Pollard A. Meningococcal Capsular Group A, C, W, and Y Conjugate Vaccines. In: Plotkin S, Orenstein W, Offit P, eds. *Plotkin's Vaccines.* 7th ed. Elsevier; 2018:619–43.

Granoff D, Pollard A, Harrison L. Meningococcal Capsular Group B Vaccines. In: Plotkin SA, Orenstein WA, Offit PA, eds. *Plotkin's Vaccines*. 7th ed. Elsevier; 2018:644–62.

McNamara L, Blain. Meningococcal Disease. In: Roush S, Baldy L, Kirkconnell Hall M, eds. Manual for the Surveillance of Vaccine-Preventable Diseases. Page last reviewed December 2019. Available at: https://www.cdc.gov/vaccines/pubs/surv-manual/chpt08-mening.html. Accessed September 1, 2020.

McNamara L, Potts C, Blain A, et al. Detection of Ciprofloxacin-Resistant, β-Lactamase–Producing *Neisseria meningitidis* Serogroup Y Isolates — United States, 2019–2020. *MMWR* 2020;69(24):735–9.

Mariel Marlow, PhD, MPH; Penina Haber, MPH; Carole Hickman, PhD; and Manisha Patel, MD, MS

Mumps is an acute viral illness. Parotitis and orchitis were described by Hippocrates in the 5th century BCE. In 1934, Claud Johnson and Ernest Goodpasture showed that mumps could be transmitted from infected patients to rhesus monkeys and demonstrated that mumps was caused by a filterable agent present in saliva. This agent was shown to be a virus in 1935. Mumps was one of the most common causes of aseptic meningitis and sensorineural hearing loss in childhood in the United States until the introduction of a vaccine in 1967. In 1971, mumps vaccine was licensed in the United States as a combined measles, mumps, and rubella (MMR) vaccine. In 2005, a combination measles, mumps, rubella, and varicella (MMRV) vaccine was licensed.

During World War I, only influenza and gonorrhea were more common than mumps as causes of hospitalization among soldiers. A successful 2-dose vaccination program in the United States led to a greater than 99% reduction in the number of mumps cases reported annually. However, starting in 2006, there has been an increase in mumps cases and outbreaks, particularly in close-contact settings, with many occurring among fully vaccinated persons.

Mumps

- Acute viral illness
- Parotitis and orchitis described by Hippocrates in 5th century BCE
- Viral etiology described by Johnson and Goodpasture in 1934
- Before vaccine, one of the most common causes of aseptic meningitis and hearing loss among children and hospitalization among military
- Vaccination led to over 99% reduction in mumps cases

Mumps Virus

Mumps virus is a paramyxovirus in the same group as parainfluenza and Newcastle disease viruses, which 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, semen, breastmilk, and infected tissues of patients with mumps.

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

Mumps Virus

- Paramyxovirus (RNA)
- Rapidly inactivated by chemical agents, heat, and ultraviolet light

Pathogenesis

The virus is acquired by respiratory droplet transmission. It replicates in the nasopharynx and regional lymph nodes. During viremia, the virus spreads to multiple tissues, including the meninges, salivary glands, pancreas, testes, and ovaries. Inflammation in infected tissues leads to characteristic symptoms of parotitis and other complications such as orchitis and aseptic meningitis.

Mumps Pathogenesis

- Respiratory transmission of virus
- Replication in nasopharynx and regional lymph nodes
- Multiple tissues infected during viremia

Mumps Clinical Features

- Incubation period usually 16 to 18 days (range, 12 to 25 days)
- Nonspecific prodrome of myalgia, malaise, headache, low-grade fever
- Typically presents as parotitis
- May presents with respiratory symptoms or be subclinical

Clinical Features

The incubation period of mumps is usually 16 to 18 days but can range from 12 to 25 days. The prodromal symptoms are nonspecific and include myalgia, anorexia, malaise, headache, and low-grade fever.

Mumps typically presents as parotitis (i.e., swelling of the parotid gland) or other salivary gland swelling lasting about 5 days. Parotitis may be unilateral or bilateral, and swelling of any combination of single or multiple salivary glands may be present. Parotitis may first be noted as earache and tenderness on palpation of the angle of the jaw. Emergence of contralateral or same side parotitis within weeks to months after apparent recovery has been described. Mumps infection may present only with nonspecific or primarily respiratory symptoms or may be a subclinical infection. Before the introduction of the mumps vaccine, approximately 15% to 24% of infections were asymptomatic. The frequency of asymptomatic infection in vaccinated persons is unknown, but mumps is generally milder among vaccinated persons.

Mumps virus is the only infectious agent known to cause epidemic parotitis. Cases of mumps reinfection have been reported.

Mumps Complications

- Orchitis, oophoritis, mastitis, pancreatitis, hearing loss, meningitis, and encephalitis
- More common among adults than children
- Less likely in vaccinated persons compared to unvaccinated persons
- Meningitis, encephalitis, pancreatitis, and hearing loss 1% or less among infected persons in the postvaccine era

Complications

Complications of mumps occur with or without parotitis or other salivary gland swelling and generally include orchitis, oophoritis, mastitis, pancreatitis, hearing loss, meningitis, and encephalitis. Nephritis, myocarditis and other sequelae, including paralysis, seizures, cranial nerve palsies, and hydrocephalus, in mumps patients have also been reported but are rare. Complications associated with mumps infection are usually more common among adults than children. Vaccinated persons are less likely to have mumps complications than unvaccinated persons.

Orchitis is the most common complication in post-pubertal males, occurring in approximately 30% of unvaccinated and 6% of vaccinated post-pubertal males. With mumps-associated orchitis, 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 multiple weeks. About half of patients with mumps orchitis develop testicular atrophy of the affected testis. While there is a theoretical risk for sterility based on the pathogenesis of the disease, no study has demonstrated a risk for sterility in men with mumps orchitis compared to those without mumps orchitis.

In the prevaccine era, oophoritis and mastitis had been reported in 7% and 30%, respectively, of post-pubertal women with mumps. Among vaccinated post-pubertal women, oophoritis

and mastitis are reported in 1% or fewer of mumps patients. Oophoritis may mimic appendicitis. Among unvaccinated patients, clinical aseptic meningitis occurred in up to 10%, pancreatitis in up to 4%, and sensorineural hearing loss in up to 4%. Meningitis is usually mild. Hearing loss is usually transient but may be permanent.

In the postvaccine era, among all persons infected with mumps, reported rates of meningitis, encephalitis, pancreatitis, and hearing loss (either transient or permanent) have all been 1% or less.

Permanent sequelae and death are very rare in both vaccinated and unvaccinated patients.

Laboratory Testing

The diagnosis of mumps is usually suspected based on clinical presentation, in particular the presence of parotitis. However, if mumps is suspected, laboratory testing should be performed. Other infectious causes of parotitis that may also be tested as part of the differential diagnosis include Epstein-Barr virus, cytomegalovirus, parainfluenza virus types 1 and 3, influenza A virus (most commonly H3N2), enteroviruses, lymphocytic choriomeningitis virus, human immunodeficiency virus (HIV), and non-tuberculous mycobacterium.

Mumps is confirmed by reverse transcriptase-polymerase chain reaction (RT-PCR) or viral culture from buccal/oral or urine specimens. A negative RT-PCR or viral culture in a person with clinically compatible mumps symptoms does not rule out mumps as a diagnosis.

Acute mumps infection can be detected by the presence of serum mumps IgM. However, this test cannot be used to confirm a diagnosis of mumps. IgM response may be transient, delayed, or not detected. This may be because of previous contact with mumps virus either through vaccination or natural infection. A negative IgM in a person with clinically compatible mumps symptoms does not rule out mumps as a diagnosis. False negatives are common so results should be interpreted with caution. Collection of serum 3 to 10 days after parotitis onset improves the ability to detect IgM.

Acute mumps infection can also be detected by a significant rise in IgG antibody titer between acute and convalescent-phase serum specimens, also known as IgG seroconversion. However, this test cannot be used to confirm a diagnosis of mumps. False positive results can occur in both unvaccinated and vaccinated persons because assays may be affected by other diagnostic entities that cause parotitis. In addition, false negative results can occur in vaccinated and unvaccinated persons. By the onset of symptoms, in

someone who is vaccinated or had previous infection, the acute-phase IgG may already be elevated, and therefore a 4-fold rise cannot be detected when compared to the convalescent-phase serum sample.

Laboratory testing can confirm the presence of mumps vaccine virus in a recently vaccinated and potentially exposed individual.

Mumps Epidemiology

- Reservoir
  - Human
- Transmission
  - Infectious respiratory droplet secretions
  - Saliva
- Temporal pattern
  - No temporal pattern
- Communicability
  - 2 days before through 5 days after onset of parotitis

Mumps Secular Trends in the United States

- About 152,000 cases reported in 1968
- Rapid decrease in cases after introduction of vaccine, but resurgence in mid-1980s among persons age 10 through 19 years
- Measles occurrence among vaccinated school-aged children in the 1980s led to recommendations for a second dose
- After 2-dose recommendation was introduced, mumps cases steadily declined from 1989 until 2004
- Increase in mumps cases since 2006 with most cases in persons fully vaccinated

Epidemiology

Occurrence

Mumps occurs worldwide, with 500,000 cases reported on average annually.

Reservoir

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

Transmission

Mumps is spread through infectious respiratory droplet secretions and saliva.

Temporal Pattern

Mumps is reported throughout the year.

Communicability

Mumps contagiousness is similar to that of influenza and rubella but is less than that for measles or varicella. Although mumps virus has been isolated from 7 days before to 9 days after parotitis onset, the highest percentage of positive isolations and the highest virus loads occur closest to parotitis onset and decrease rapidly thereafter. Mumps is therefore most infectious, and most transmission likely occurs, in the several days before and after parotitis onset. Mumps is considered infectious from 2 days before through 5 days after onset of parotitis. Transmission also likely occurs from persons with asymptomatic infections and from persons with prodromal symptoms.

Secular Trends in the United States

Mumps became nationally notifiable in 1968 with about 152,000 cases reported. After the use of the mumps vaccine, cases began to decrease rapidly. By 1985, fewer than 3,000 cases were reported annually.

In the mid-1980s there was a relative resurgence of mumps with approximately 13,000 cases reported in 1987. The highest incidence of mumps during the resurgence was among older school-age and college-age youth (age 10 through 19 years), who were born before routine mumps vaccination was recommended. 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.

After two doses of measles, mumps, and rubella vaccine were recommended in 1989 for school-age children for improved measles control, the number of reported mumps cases steadily declined, from approximately 5,700 cases in 1989 to fewer than 300 cases in 2004.

Since 2006, there has been an increase in the number of reported mumps cases. Most cases reported in 2006 and 2009-2010 were associated with a few large, localized outbreaks. However, since 2014, more than 1,000 mumps cases have been reported each year, and in 2019 nearly every state reported mumps cases. During January 2016 through June 2017, 150 outbreaks were reported in 37 states, accounting for more than 9,000 cases. Since 2006, most cases have been in persons who previously received 2 doses of MMR vaccine. Most outbreaks involved close-contact settings, such as households, schools, universities, athletics teams and facilities, church groups, workplaces, large parties, and other events.

Among children born during 2016–2017, 90.7% received measles, mumps, and rubella-containing vaccine by age 24 months; this was not statistically significantly different from the coverage of 90.3% for children born during 2014–2015.

Mumps Vaccines

The live, attenuated mumps vaccine (Jeryl Lynn strain) was licensed for use in the United States in 1967. Jeryl Lynn strain is the only mumps virus strain that has been used in mumps vaccines in the United States. In 1971, mumps vaccine was licensed as a combined measles, mumps, and rubella (MMR) vaccine. In 2005, a combination measles, mumps, rubella, and varicella (MMRV) vaccine was licensed.

Mumps Vaccines

- MMR (MMR-II)
- MMRV (ProQuad)

Mumps vaccine is available as measles, mumps, and rubella vaccine (MMR [MMR-II]) and measles, mumps, rubella, and varicella vaccine (MMRV [ProQuad]). Both MMR and MMRV vaccine contain live, attenuated viruses. Single-antigen mumps vaccine is not available in the United States. The Advisory Committee on Immunization Practices (ACIP) recommends that MMR or MMRV vaccine be used when any of the individual components is indicated.

Mumps

Mumps Vaccine Characteristics

- Live, attenuated vaccine
- Available as lyophilized powder and reconstituted with sterile, preservative-free water
- Administered by subcutaneous injection
- Contains gelatin
- Contains neomycin

Characteristics

MMR vaccine is a lyophilized preparation of measles virus vaccine live, an attenuated line of measles virus, derived from Enders' attenuated Edmonston strain and propagated in chick embryo cell culture; mumps virus vaccine live, the Jeryl Lynn strain of mumps virus propagated in chick embryo cell culture; and rubella virus vaccine live, the Wistar RA 27/3 strain of live attenuated rubella virus propagated in WI-38 human diploid lung fibroblasts. MMRV vaccine contains measles, mumps, and rubella virus of equal titer and identical to those in the MMR vaccine. The titer of Oka varicella zoster virus is higher in MMRV vaccine than in single-antigen varicella vaccine, a minimum of 9,772 plaque-forming units (PFU) versus 1,350 PFU, respectively. MMR and MMRV vaccines are supplied as a lyophilized (freeze-dried) powder and are reconstituted with sterile, preservative-free water. Both vaccines contain gelatin. MMR and MMRV vaccines are administered by the subcutaneous route. Each dose of MMR and MMRV vaccine contains neomycin as an antibiotic. It contains no adjuvant or preservative.

Mumps Vaccination Schedule

- 2 dose series at age 12 through 15 months and at age 4 through 6 years
- Minimum age for dose 1 is 12 months
- Minimum interval from dose 1 to 2 is 4 weeks for MMR and 3 months for MMRV (although a 4-week interval is valid)
- Discuss risks and benefits of MMRV versus separate MMR and VAR
  - Separate MMR and VAR vaccines preferred for dose 1 in ages 12 through 47 months
  - MMRV preferred for dose 2 and dose 1 at age 48 months or older

Vaccination Schedule and Use

MMR vaccine or MMRV vaccine can be used to implement the vaccination recommendations for prevention of measles, mumps, and rubella. MMR vaccine is licensed for use in persons age 12 months or older. MMRV vaccine is licensed for use in persons age 12 months through 12 years; MMRV vaccine should not be administered to persons age 13 years or older.

Two doses of MMR vaccine, separated by at least 4 weeks, are routinely recommended for children age 12 months or older. Dose 1 of MMR vaccine should be given at age 12 through 15 months. A second dose of MMR vaccine is recommended based on previous observations of the failure of some to generate an immune response to measles following dose 1. Dose 2 is routinely given at age 4 through 6 years, before a child enters kindergarten or first grade. All students entering school should receive 2 doses of MMR vaccine (with the first dose administered at age 12 months or older) before enrollment. Dose 2 of MMR vaccine may be administered as soon as 4 weeks after dose 1.

The minimum interval between doses of MMRV vaccine is 3 months, although when dose 2 is administered 4 weeks following dose 1, it can be considered valid. For the first dose of measles, mumps, rubella, and varicella vaccines at age 12 through 47 months, either separate MMR and varicella (VAR) vaccines, or MMRV vaccine, may be used. However, the risk of febrile seizures is about twice as high for children receiving MMRV vaccine versus separate MMR and VAR vaccines. Providers who are considering administering MMRV should discuss the benefits and risks of both vaccination options with the parents.

Unless the parent or caregiver expresses a preference for MMRV, separate MMR vaccine and VAR vaccine should be administered for the first dose in this age group. For the second dose of measles, mumps, rubella, and varicella vaccines at any age and for the first dose at age 48 months or older, the use of MMRV generally is preferred over separate injections of its equivalent component vaccines (i.e., MMR vaccine and VAR vaccine).

Vaccination of Adults

Adults born in 1957 or later should receive at least 1 dose of MMR vaccine unless they have documentation of vaccination with at least 1 dose of measles, mumps, and rubella-containing vaccine or other acceptable presumptive evidence of immunity to these three diseases. Except for health care personnel, who should have documented immunity, birth before 1957 generally can be considered acceptable evidence of immunity to measles, mumps, and rubella.

Colleges and other post-high-school educational institutions are potential high-risk areas for measles, mumps, and rubella transmission because of large concentrations of persons. Prematriculation vaccination requirements for measles immunity have been shown to significantly decrease the risk of measles outbreaks on college campuses where such requirements are implemented and enforced. All students entering colleges, universities, technical and vocational schools, and other institutions for post-high-school education should receive 2 doses of MMR vaccine or have other acceptable evidence of measles, mumps, and rubella immunity before entry.

For unvaccinated health care personnel born before 1957 who lack laboratory evidence of measles, mumps, or rubella immunity or laboratory confirmation of disease, health care facilities should have policies that offer 2 doses of MMR vaccine at the appropriate interval for measles and mumps and 1 dose of MMR vaccine for rubella, respectively. Health care facilities should also have policies for such personnel that recommend 2 doses of MMR vaccine during an outbreak of measles or mumps and 1 dose during an outbreak of rubella. This recommendation is based on serologic studies indicating that among hospital personnel born before 1957, 5% to 10% had no detectable measles, mumps, or rubella antibody. Adequate vaccination for health care personnel born during or after 1957 consists of 2 appropriately spaced MMR doses for measles and mumps, and at least 1 dose of MMR for rubella.

MMR Vaccination of Adults

- Certain persons without acceptable presumptive immunity:
  - At least 1 dose MMR for unvaccinated adults
  - 2 doses MMR for students entering colleges, universities, technical and vocational schools, and other post-high-school educational institutions
  - 2 doses MMR for measles and mumps and at least 1 dose MMR for rubella for healthcare personnel
- Healthcare personnel during an outbreak
  - 2 doses MMR for measles or mumps outbreak and 1 dose MMR for rubella outbreak

Revaccination

Measles-, mumps-, or rubella- virus-containing vaccine administered prior to age 12 months (e.g., for international travel) should not be counted as part of the 2-dose series. Children vaccinated before age 12 months should be

revaccinated with 2 doses of appropriately spaced MMR or MMRV vaccine, the first dose administered when the child is age 12 through 15 months (12 months if the child remains in an area where disease risk is high) and the second dose at least 4 weeks later.

Persons who experienced perinatal HIV infection who may have received MMR vaccine prior to the establishment of effective combined antiretroviral therapy (cART), should be revaccinated with 2 appropriately spaced doses of MMR (i.e., the dose does not count) unless they have other acceptable current evidence of immunity. MMR series should be administered once effective cART has been established for at least 6 months and there is no evidence of severe immunosuppression.

Vaccination during Mumps Outbreaks

During an outbreak, a third dose of MMR vaccine is recommended for groups determined by public health authorities to be at increased risk for acquiring mumps to improve protection against mumps disease and related complications. Public health authorities will communicate to providers which groups are at increased risk and should receive an MMR dose. Everyone who is determined to be part of the group at increased risk and does not have contraindications should receive a dose of MMR vaccine. This includes people who do not have vaccine records that prove they received two doses of MMR vaccine in the past, and people who have evidence of presumptive immunity. No additional dose is recommended for people who already received three or more doses before the outbreak.

Mumps Immunity

- Born before 1957
- Serologic evidence of mumps immunity (equivocal tests are considered negative)
  - Mumps IgG antibody does not necessarily predict protection; during an outbreak, close contacts of mumps patient(s) should not be tested for serologic evidence of immunity
- Laboratory confirmation of disease
- Documentation of adequate vaccination for mumps

Mumps Immunity

Generally, persons can be considered immune to mumps if they were born before 1957, have serologic evidence of mumps immunity (equivocal test results should be considered negative), or laboratory confirmation of disease, or have documentation of adequate vaccination for mumps.

Demonstration of mumps IgG antibody by any commonly used serologic assay is acceptable evidence of mumps immunity but does not necessarily predict protection against mumps disease. During an outbreak, close contacts of mumps patient(s) should not be tested for laboratory evidence of immunity since a positive IgG titer may indicate acute infection.

Mumps Vaccine Efficacy

- Antibodies develop in approximately 94% of recipients of a single dose
- One dose produced 78% effectiveness and two doses 88% effectiveness

Immunogenicity and Vaccine Efficacy

Mumps vaccine produces an inapparent, or mild, noncommunicable infection. Approximately 94% of recipients of a single dose develop measurable mumps antibody. Seroconversion rates are similar for single antigen mumps

vaccine, MMR vaccine, and MMRV vaccine. Postlicensure studies determined that vaccine effectiveness of one dose of mumps or MMR vaccine was 78% and two dose mumps vaccine effectiveness is 88%.

Contraindications and Precautions to Vaccination

As with other vaccines, a history of a severe allergic reaction (anaphylaxis) to a vaccine component or following a prior dose is a contraindication to further doses. Moderate or severe acute illness (with or without fever) in a patient is considered a precaution to vaccination, although persons with minor illness may be vaccinated.

MMR and MMRV vaccines both contain minute amounts of neomycin and gelatin. Persons with alpha-gal allergy may wish to consult their physician before receiving a vaccine that contains gelatin.

Severe immunocompromise (e.g., from hematologic and solid tumors, receipt of chemotherapy, congenital immunodeficiency, long-term immunosuppressive therapy or patients with HIV infection who are severely immunocompromised) is a contraindication for MMR and MMRV vaccination. If the person's level of immunocompetence is uncertain, the decision to vaccinate should be made by the health care provider that prescribed the immunosuppressive medication for those patients whom immunocompromise is due to medication. Patients who have not received chemotherapy for at least 3 months, whose disease remains in remission, and who have restored immunocompetence, may receive MMR or MMRV vaccine. Healthy, susceptible close contacts of severely immunocompromised persons should be vaccinated.

Persons receiving systemic high-dose corticosteroid therapy (2 milligrams per kilogram of body weight or more per day or 20 milligrams or more per day of prednisone) for 14 days or more should not receive MMR or MMRV vaccine because of concern about vaccine safety. MMR or MMRV should not be administered for at least 1 month after cessation of systemic high-dose corticosteroid therapy. Although persons receiving high doses of systemic corticosteroids daily or on alternate days for less than 14 days generally can receive MMR or MMRV immediately after cessation of treatment, some experts prefer waiting until 2 weeks after completion of therapy.

Available data indicate that vaccination with MMR has not been associated with severe or unusual adverse reactions in HIV-infected persons who are not severely immunosuppressed, although antibody responses have been variable. MMR vaccine is recommended for susceptible HIV-infected persons age 12 months or older with no evidence of current

Mumps Vaccine Contraindications and Precautions

- Contraindication
  - Severe allergic reaction to vaccine component or following a prior dose
  - Severe immunocompromise
  - Systemic high-dose corticosteroid therapy for 14 days or more
  - HIV infection, regardless of immunocompetence status*
  - Family history of congenital or heredity immunodeficiency in first-degree relatives
  - Pregnancy
- Precaution
  - Moderate or severe acute illness
  - Alpha-gal allergy (consult with physician)
  - Receipt of antibody-containing blood products (wait 3 to 11 months to vaccinate)
  - History of thrombocytopenic purpura or thrombocytopenia
  - Need for tuberculin skin testing or interferon-gamma release assay testing
  - Simultaneous use of aspirin or aspirin-containing products*
  - Personal or family history of seizures of any etiology*
  - Receipt of specific antiviral drugs 24 hours before vaccination*

*MMRV only

severe immunosuppression ("no evidence of current severe immunosuppression" is defined as CD4 percentages greater than or equal to 15% for 6 months or longer for persons age 5 years or younger; and CD4 percentages greater than or equal to 15% and CD4 count greater than or equal to 200 cells/mm^3 for 6 months or longer for persons older than age 5 years). MMR vaccine is not recommended for HIV-infected persons with evidence of severe immunosuppression.

MMRV is not approved for and should not be administered to a person known to be infected with HIV.

A family history of congenital or hereditary immunodeficiency in first-degree relatives (e.g., parents and siblings) is a contraindication for MMR or MMRV vaccine unless the immune competence of the potential vaccine recipient has been substantiated clinically or verified by a laboratory.

A history of thrombocytopenic purpura or thrombocytopenia is a precaution for MMR and MMRV vaccine. Such persons may be at increased risk for developing clinically significant thrombocytopenia after MMR or MMRV vaccination.

Simultaneous use of aspirin or aspirin-containing products is a precaution for MMRV vaccine due to the varicella component. The manufacturer recommends that vaccine recipients avoid the use of salicylates for 6 weeks after receiving MMRV vaccine because of the association between aspirin use and Reye syndrome following chickenpox.

A personal or family (i.e., sibling or parent) history of seizures of any etiology is a precaution for MMRV vaccine but not MMR. Children with a personal or family history of seizures of any etiology should ideally be vaccinated with separate MMR and VAR vaccines because the risks for using MMRV vaccine in this group of children generally outweigh the benefits.

MMR vaccine may be administered to egg-allergic persons without prior routine skin testing or the use of special protocols.

Spacing Considerations

The effect of the administration of antibody-containing blood products (e.g., immune globulin, whole blood or packed red blood cells, or intravenous immune globulin) on the response to MMR or MMRV vaccine is unknown. Because of the potential inhibition of the response to vaccination by passively transferred antibodies, neither MMR vaccine nor MMRV vaccine (nor VAR vaccine) should be administered for 3 to 11 months after receipt of antibody-containing blood products. The interval between the antibody-containing blood product and receipt of MMR or MMRV vaccine is determined by the type of product administered. Antibody-containing products should not be given for 2 weeks following vaccination unless

the benefits exceed those of the vaccine. In such cases, vaccine recipients should either be revaccinated later at the appropriate intervals (ranging 3 to 11 months) or tested for immunity and revaccinated if seronegative.

Need for tuberculin skin testing or interferon-gamma release assay (IGRA) testing is a precaution for MMR and MMRV vaccine. Measles vaccine (and possibly mumps, rubella, and varicella vaccines) may transiently suppress the response to tuberculin skin test (TST) in a person infected with Mycobacterium tuberculosis. TST and measles-containing vaccine may be administered at the same visit if necessary. Simultaneously administering TST and measles-containing vaccine does not interfere with reading the TST result at 48 to 72 hours and ensures that the person has received measles vaccine. If the measles-containing vaccine has been administered recently, TST screening should be delayed for at least 4 weeks after vaccination.

Receipt of specific antiviral drugs (e.g., acyclovir, famciclovir, or valacyclovir) 24 hours before vaccination is a precaution for MMRV vaccine due to the varicella component. These drugs should be avoided for 14 days after vaccination.

Vaccination in Pregnancy

Pregnancy is a contraindication for MMR or MMRV vaccine. Pregnancy should be avoided for 4 weeks following MMR or MMRV vaccine. Close contact with a pregnant woman is not a contraindication to MMR or MMRV vaccination of the contact.

If a pregnant woman inadvertently receives MMR or MMRV vaccine, termination of pregnancy is not recommended because the risk to the fetus appears to be extremely low. Instead, individual counseling for these women is recommended.

Vaccine Safety

Studies have shown MMR and MMRV vaccines are safe and well-tolerated. The National Academy of Medicine, formerly called the Institute of Medicine, reviewed the evidence between MMR vaccination and certain adverse events. The experts determined that evidence supports a causal relation between MMR vaccination and anaphylaxis, febrile seizures, thrombocytopenic purpura, transient arthralgia, and measles inclusion body encephalitis in persons with demonstrated immunodeficiencies.

Most adverse events reported following MMR vaccination (such as fever and rash) are attributable to the measles component. After MMR vaccination, 5% to 15% of susceptible persons develop a temperature of 103°F (39.4°C) or higher, usually occurring 7 to 12 days after vaccination and generally lasting 1 or 2 days. Most persons with fever do not have other symptoms. MMR vaccine is associated with a very small risk

Mumps Vaccine Safety

MMR

- Fever of 103°F (39.4°C) or higher
  - 5%–15%
- Rash
  - 5%
- Febrile seizures
  - 1 in every 3,000 to 4,000 doses
- Anaphylactic reactions
  - 1.8 to 14.4 cases per million doses
- Arthralgias and other joint symptoms
  - 25% (adult women)

MMRV

- Fever of 102°F or higher
  - 21.5%
- Febrile seizures
  - 1 additional per 2,300 to 2,600 children age 12 through 23 months

of febrile seizures; approximately one case for every 3,000 to 4,000 doses of MMR vaccine administered. The febrile seizures typically occur 6 to 14 days after vaccination and do not appear to be associated with any long-term sequelae. Children with a personal or family history of febrile seizures or family history of epilepsy might be at increased risk for febrile seizures after MMR vaccination.

MMR vaccine may cause a transient rash in approximately 5% of vaccine recipients, usually appearing 7 to 10 days after vaccination. Laboratory testing can confirm the presence of measles or mumps vaccine virus in a recently vaccinated and potentially exposed individual.

Allergic reactions following the administration of MMR vaccine are rare. Most of these are minor and consist of a wheal and flare or urticaria at the injection site. Immediate, anaphylactic reactions to MMR vaccine occur in 1.8 to 14.4 cases per million doses.

Arthralgias and other joint symptoms are reported in up to 25% of adult women following MMR vaccination and are associated with the rubella component. Transient lymphadenopathy sometimes occurs following receipt of MMR or other rubella-containing vaccine, and parotitis has been reported rarely (less than 1%) following receipt of MMR or other mumps-containing vaccine.

Rarely, MMR vaccine may cause thrombocytopenia within two months after vaccination. The clinical course of these cases is usually transient and benign, although hemorrhage occurs rarely. Based on case reports, the risk for MMR vaccine-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.

Measles inclusion body encephalitis has been documented after measles vaccination in persons with immune deficiencies. The illness is also known to occur within 1 year after initial infection with wild-type measles virus and has a high death rate. In the cases after MMR vaccination, the time from vaccination to development of measles inclusion body encephalitis was 4–9 months, consistent with development of measles inclusion body encephalitis after infection with wild-type measles virus.

In MMRV vaccine prelicensure studies conducted among children age 12 to 23 months, fever (reported as abnormal or elevated greater than or equal to 102°F oral equivalent) was observed 5 to 12 days after vaccination in 21.5% of MMRV vaccine recipients compared with 14.9% of MMR vaccine and VAR vaccine recipients. Two postlicensure studies indicated that one additional febrile seizure per 2,300 to 2,600 children age 12 through 23 months occurred 5 to 12 days after the first dose of

MMRV vaccine, compared with children who had received the first dose of MMR vaccine and VAR vaccine administered as separate injections at the same visit. Data from postlicensure studies do not suggest that this increased risk exists for children age 4 to 6 years receiving the second dose of MMRV vaccine.

Multiple studies, as well as a National Academy of Medicine Vaccine Safety Review, refute a causal relationship between autism and MMR vaccine or between inflammatory bowel disease and MMR vaccine.

Vaccine Storage and Handling

For MMR-II and Proquad storage and handling specifics, refer to the manufacturer. For complete information on storage and handling best practices and recommendations, please refer to CDC's Vaccine Storage and Handling Toolkit, www.cdc.gov/vaccines/hcp/admin/storage/toolkit/storage-handling-toolkit.pdf.

Surveillance and Reporting for Mumps

Mumps became nationally notifiable in the United States in 1968. For information on guidance for state and local health department staff who are involved in surveillance activities for vaccine-preventable diseases, please consult the *Manual for the Surveillance of Vaccine-Preventable Diseases*, www.cdc.gov/vaccines/pubs/surv-manual/chapters.html.

Acknowledgements

The editors would like to acknowledge Amy Parker Fiebelkorn and Mona Marin for their contributions to this chapter.

NOTES

NOTES

Selected References

CDC. Prevention of measles, rubella, congenital rubella syndrome, and mumps, 2013: summary recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2013;62(No. RR-4):1–34.

Clemmons N, Hickman C, Lee A, et al. Mumps. In Roush S, Baldy L, Kirkconnell Hall M, eds. *CDC Manual for the Surveillance of Vaccine-Preventable Diseases*. Atlanta, GA: US Department of Health and Human Services, CDC; 2018.

CDC. Mumps. https://www.cdc.gov/mumps/health-departments/MMR3.html. Accessed October 10, 2020.

CDC. Prevention of measles, rubella, congenital rubella syndrome, and mumps, 2013: summary recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2013;62(No. RR-4):1–34.

CDC. Recommendations of the Advisory Committee on Immunization Practices for use of a third dose of mumps virus-containing vaccine in persons at increased risk for mumps during an outbreak. *MMWR* 2018;67(1):33–8.

CDC. Recommendation of the Public Health Service Advisory Committee on Immunization Practices: mumps vaccine. *MMWR* 1977;26:393–4.

CDC. Updated recommendations for isolation of persons with mumps. *MMWR* 2008. 57(40):1103–5.

CDC. Use of combination measles, mumps, rubella, and varicella vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2010;59(No. RR-3):1–12.

Rubin S, Eckhaus M, Rennick L, et al. Molecular biology, pathogenesis and pathology of mumps virus. *J Pathol*. 2015;235(2):242–52.

Kutty P, Kyaw M, Dayan, G, et al. Guidance for isolation precautions for mumps in the United States: a review of the scientific basis for policy change. *Clin Infect Dis* 2010;50(12):1619–28.

Marlow M, Marin M, Moore K, et al. CDC Guidance for Use of a Third Dose of MMR Vaccine During Mumps Outbreaks. *J Public Health Manag Pract*. 2019;26(2):109–15.

Rubin S. Mumps Vaccines. In: Plotkin S, Orenstein W, Offit P, et al., eds. Plotkin's *Vaccines*. 7th ed. Elsevier;2018:663–88.

WHO. *Mumps reported cases.* http://apps.who.int/immunization_monitoring/globalsummary/timeseries/tsincidencemumps.html. Accessed May, 28 2020.

Fiona P. Havers, MD, MHS; Pedro L. Moro, MD, MPH; Susan Hariri, PhD; and Tami Skoff, MS

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 by Guillaume de Baillou. The organism was first isolated by Jules Bordet and Octave Gengou in 1906.

In the 20th century, pertussis was one of the most common childhood diseases and a major cause of childhood mortality in the United States. Before the availability of pertussis vaccine in the 1940s, more than 200,000 cases of pertussis were reported annually. Since widespread use of the vaccine began, incidence has decreased more than 75% compared with the prevaccine era.

Pertussis remains a major health problem among children worldwide. Data from a recent modeling study suggest that more than 24 million new pertussis cases occurred globally among children younger than age 5 years in 2014 and caused an estimated 160,700 deaths.

Pertussis

- Acute infectious disease caused by *Bordetella pertussis*
- Outbreaks first described in 16th century
- *Bordetella pertussis* isolated in 1906
- More than 200,000 cases annually in the United States in prevaccine era

Bordetella pertussis

B. pertussis is a small, aerobic gram-negative rod. It requires special media for isolation.

B. pertussis produces multiple antigenic and biologically active products, including pertussis toxin (PT), filamentous hemagglutinin (FHA), agglutinogens, adenylate cyclase, pertactin, and tracheal cytotoxin. These products are responsible for the clinical features of pertussis disease. An immune response to one or more of these products produces immunity following infection. Immunity following *B. pertussis* infection is not permanent.

Bordetella pertussis

- Aerobic gram-negative bacteria
- Antigenic and biologically active components:
  - Pertussis toxin (PT)
  - Filamentous hemagglutinin (FHA)
  - Agglutinogens
  - Adenylate cyclase
  - Pertactin
  - Tracheal cytotoxin

Pathogenesis

Pertussis is primarily a toxin-mediated disease. The bacteria attach to the cilia of the respiratory epithelial cells, produce toxins that paralyze the cilia, and cause inflammation of the respiratory tract, which interferes with the clearing of pulmonary secretions. Pertussis antigens appear to allow the organism to evade host defenses in that lymphocytosis is promoted but chemotaxis is impaired.

Previously it was thought that *B. pertussis* did not invade the tissues. However, studies have shown the bacteria to be present in alveolar macrophages.

Pertussis Pathogenesis

- Primarily a toxin-mediated disease
- Bacteria attach to cilia of respiratory epithelial cells
- Toxins cause inflammation which interferes with clearance of pulmonary secretions
- Pertussis antigens allow evasion of host defenses

Pertussis Clinical Features

- Incubation period 7 through 10 days (range, 4 through 21 days)
- Catarrhal stage: Insidious onset, similar to the common cold
  - 1-2 weeks
- Paroxysmal stage: More severe cough and may experience paroxysms of numerous, rapid coughs
  - 1-6 weeks
- Convalescence stage: Gradual recovery
  - weeks to months

Clinical Features

The incubation period of pertussis is commonly 7 through 10 days, with a range of 4 through 21 days. The clinical course of the illness is divided into three stages: catarrhal, paroxysmal, and convalescent.

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 to 2 weeks, the second, or paroxysmal, stage, begins. Fever is generally minimal throughout the course of the illness.

It is during the paroxysmal stage that the diagnosis of pertussis is usually suspected. Characteristically, the patient might have 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. Children and young infants, especially, might appear very ill and distressed. Vomiting and exhaustion might follow the episode. The person does not appear to be ill between attacks.

Paroxysmal attacks generally occur more frequently at night, with an average of 15 attacks per 24 hours. During the first 1 or 2 weeks of this paroxysmal stage, the attacks might 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 age 6 months may not have the strength to have a whoop, but they can have paroxysms of coughing. Additionally, the classic whoop might not be present in persons with milder disease.

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

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

Even though the disease may be milder in older persons, those who are infected may still transmit the disease to other susceptible persons, including unimmunized or incompletely immunized infants. An adult, adolescent, or older school-age

child is often found to be the first case in a household with multiple pertussis cases and is often the source of infection for young infants.

Complications

The most common complication, and the cause of most pertussis-related deaths, is secondary bacterial pneumonia. Young infants are at highest risk for developing pertussis-associated complications. Data from 2000–2017 indicate that pneumonia occurred in 13.2% of all reported pertussis cases, and among 18.6% of infants younger than age 6 months.

Neurologic complications such as seizures and encephalopathy may occur as a result of hypoxia from coughing, or possibly from pertussis toxin. Neurologic complications of pertussis are more common among infants.

Other less serious complications of pertussis include otitis media, anorexia, and dehydration. Complications resulting from pressure effects of severe paroxysms include pneumothorax, epistaxis, subdural hematomas, hernias, and rectal prolapse.

Between 2000 and 2017, 307 deaths from pertussis were reported to CDC; children younger than age 2 months accounted for 84.0% of these deaths. During the same time period, among infants, the annual mean number of pertussis cases, hospitalizations, and deaths were 2,957 (range 1,803 to 4,994), 1,122 (range 544 to 1,938), and 15 (range 3 to 35), respectively.

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

Pertussis Complications

- Most common complication and cause of death is secondary bacterial pneumonia
- Young infants at highest risk
- Neurologic complications—seizures, encephalopathy
- Less serious complications—otitis media, anorexia, dehydration
- 307 deaths between 2000 and 2017

Laboratory Testing

The diagnosis of pertussis is based on a clinical history of signs and symptoms, as well as a variety of laboratory tests (e.g., culture, polymerase chain reaction [PCR], and serology).

Culture is considered the gold standard laboratory test and is the most specific of the laboratory tests for pertussis. However, fastidious growth requirements make *B. pertussis* difficult to culture. The yield of culture can be affected by specimen collection, transportation, and isolation techniques. Specimens from the posterior nasopharynx, not the throat, should be obtained using polyester, rayon, nylon, or calcium alginate (not cotton) swabs. Isolation rates are highest during the first 2 weeks of illness (catarrhal and early paroxysmal stages). Cultures are less likely to be positive if performed later in the course of illness (more than 2 weeks after cough onset) or on specimens from persons who have received antibiotics or who have been

vaccinated. Since adolescents and adults have often been coughing for several weeks before they seek medical attention, it is often too late for culture to be useful.

PCR is a rapid test and has excellent sensitivity. PCR tests vary in specificity, so obtaining culture confirmation of pertussis for at least one possible case is recommended any time there is suspicion of a pertussis outbreak. Results should be interpreted along with the clinical symptoms and epidemiological information. PCR should be performed on nasopharyngeal specimens taken at 0 to 3 weeks following cough onset but may provide accurate results for up to 4 weeks of cough in infants or unvaccinated persons. After the fourth week of cough, the amount of bacterial DNA rapidly diminishes, which increases the risk of obtaining false negative results. PCR assay protocols that include multiple targets allow for Bordetella speciation. False positive results may be obtained because of contamination in the laboratory or during specimen collection. Direct comparison with culture is necessary for validation, and the use of multiple targets is recommended to distinguish *B. pertussis* from other *Bordetella species*.

Serologic testing is generally more useful for diagnosing pertussis during the later phase of disease when both culture and PCR are likely to be negative. For the CDC/FDA single-point serologic assay, the optimal timing for specimen collection is 2 to 8 weeks following cough onset, when the antibody titers are at their highest. However, serology may be performed on specimens collected up to 12 weeks following cough onset. Many state public health labs have included this assay as part of their testing regimen for pertussis.

Commercially, there are many different serologic tests used in the United States with unproven or unknown clinical accuracy. CDC is actively engaged in better understanding the usefulness of these commercially available assays.

Because direct fluorescent antibody testing of nasopharyngeal secretions has been demonstrated in some studies to have low sensitivity and variable specificity, such testing should not be relied on as a criterion for laboratory confirmation.

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

Medical Management

The medical management of pertussis patients is primarily supportive, although antibiotics are of some value if administered early. This therapy eradicates the organism from secretions, thereby decreasing communicability and may

modify the course of the illness if initiated early (i.e., during the first 1 to 2 weeks of cough before coughing paroxysms begin). Recommended antibiotics are azithromycin, clarithromycin, and erythromycin. Trimethoprim-sulfamethoxazole can also be used.

Preventive Measures

Immunity following pertussis is not permanent. Unvaccinated or incompletely vaccinated persons recovering from pertussis should begin or complete active immunization with DTaP or Tdap as indicated.

Vaccination history of close contacts of pertussis patients should also be assessed. An antibiotic effective against pertussis should be administered to all close contacts of persons with pertussis, regardless of age and vaccination status. All close contacts younger than age 7 years who have not completed the 3-dose primary vaccination series of a pertussis-containing vaccine and the first booster dose usually given at age 15 through 18 months should complete the series according to the minimum intervals. Close contacts who are age 4 through 6 years and who have not yet received the second booster dose of pertussis-containing vaccine (usually the fifth dose of DTaP [diphtheria and tetanus toxoids and acellular pertussis vaccine]) should be vaccinated.

Epidemiology

Occurrence

Pertussis occurs worldwide.

Reservoir

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

Transmission

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

Temporal Pattern

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

Communicability

Pertussis is highly communicable, as evidenced by secondary attack rates of 80% among susceptible household contacts. Persons with pertussis are infectious from the beginning of

Pertussis Epidemiology

- Reservoir
  - Humans
- Transmission
  - Person-to-person through respiratory droplets or contact with airborne droplets
  - Exposure to fomites
- Temporal pattern
  - No distinct seasonal pattern, but may increase in the summer and fall
- Communicability
  - Highly communicable
  - Infectious from catarrhal stage through third week of paroxysms

the catarrhal stage through the third week after the onset of paroxysms or until 5 days after the start of effective antimicrobial treatment.

Pertussis Secular Trends in the United States

- Average of 175,000 cases per year before vaccine
- Cases gradually declined after vaccine introduced in 1940s
- Between 1980 and 1990, 2,900 reported cases per year
- Incidence gradually increasing in United States since late 1980s with large epidemic peaks since mid-2000s
  - Waning of vaccine-induced immunity may play a role in increase

Secular Trends in the United States

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

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

Reported pertussis incidence has been gradually increasing in the United States since the late 1980s and early 1990s, and large epidemic peaks in disease have been observed since the mid-2000s. A total of 48,277 pertussis cases were reported in 2012, the largest number reported since the mid-1950s. There are likely many factors contributing to the observed increase in reported disease. These include changes in diagnostic testing, heightened recognition and reporting of pertussis cases, and molecular changes in the organism. However, waning of vaccine-induced immunity is thought to play a key role in countries, including the United States, that have transitioned to acellular vaccines in the 1990s.

Infants younger than age 1 year continue to have the highest rates of pertussis. In 2018, pertussis incidence per 100,000 was 72.3 in infants younger than age 6 months and 32.7 in infants age 6 to 12 months, compared to 1.4 in persons age 20 years or older. However, the epidemiology of pertussis has changed since the late 1980s, and an increasing burden of reported cases in the United States is now occurring among fully vaccinated children and adolescents. Between 2000–2006, the second highest average annual incidence rate was reported among adolescents age 11 through 18 years (13.1 per 100,000 population). Between 2007 and 2014, children age 7 through 10 years had the second highest average annual incidence rate (28.3 cases per 100,000 population). While the incidence of pertussis in children age 7 through 10 years and 11 through 18 years was comparable between 2015 and 2016, the rate of disease in adolescents age 11 through 18 years once again surpassed the rates of disease among children age 7 through 10 years during this period. The observed changes in pertussis epidemiology in recent years coincide with the transition to

acellular vaccines in the United States and the aging of the first acellular-primed birth cohorts, suggesting a key role of waning immunity.

Among children born during 2016–2017, 93.3% had received at least 3 doses of DTaP vaccine by age 24 months, and 80.6% had received at least 4 doses of DTaP vaccine by age 24 months. Although Tdap coverage among adolescents age 13 through 17 years reached 90.2% in 2019, coverage remains low among adults (31.7% in 2017).

Pertussis-containing Vaccines

Whole-cell pertussis vaccines were first licensed in the United States in 1914 and were available as a combined vaccine with diphtheria and tetanus toxoids (as DTP) in 1948. Based on controlled efficacy trials conducted in the 1940s and on subsequent observational efficacy studies, a series of 4 doses of whole-cell DTP vaccine was 70% to 90% effective in preventing serious pertussis disease. Local reactions such as redness, swelling, and pain at the injection site occurred following up to 50% of doses of whole-cell DTP vaccines. Fever and other mild systemic events were also common. Concerns about safety led to the development of more purified (acellular) pertussis vaccines, which are associated with a lower frequency of adverse reactions. No DTP vaccines are currently licensed in the United States.

Pertussis-containing Vaccines

- DTaP (Daptacel and Infanrix)
- Tdap (Adacel and Boostrix)
- DTaP-HepB-IPV (Pediarix)
- DTaP-IPV/Hib (Pentacel)
- DTaP-IPV (Kinrix and Quadracel)
- DTaP-IPV-Hib-HepB (Vaxelis)

Acellular pertussis vaccine is combined with tetanus toxoid and diphtheria toxoid as DTaP (Infanrix and Daptacel) or Tdap (Boostrix and Adacel). DTaP and Tdap contain the same pertussis components, but Tdap contains a reduced quantity of some pertussis antigens and diphtheria toxoid. Boostrix contains a reduced quantity of tetanus toxoid compared to Infanrix.

Children younger than age 7 years should receive DTaP vaccine or DT vaccine (in instances where the pertussis vaccine component is contraindicated or where the physician decides that pertussis vaccine is not to be administered). Persons age 7 years or older should receive the Td vaccine or Tdap vaccine (Tdap would be off-label for children age 7 through 9 years, but is still recommended by ACIP), even if they have not completed a series of DTaP or DT. Tdap (Boostrix) is approved for persons age 10 years or older; Tdap (Adacel) is approved for persons age 10 through 64 years.

There are five combination vaccines that contain DTaP vaccine. DTaP-HepB-IPV (Pediarix) is licensed for the first 3 doses of the DTaP series among children age 6 weeks through 6 years. DTaP-IPV/Hib (Pentacel) is licensed for the first 4 doses of the component vaccines among children age 6 weeks through 4 years. DTaP-IPV (Kinrix) is licensed only for the fifth dose of DTaP and fourth dose of IPV among children age 4 through 6 years.

DTaP-IPV (Quadracel) is licensed only for the fourth dose of DTaP and fourth or fifth dose of IPV among children age 4 through 6 years. DTaP-IPV-Hib-HepB (Vaxelis) is licensed for use in children age 6 weeks through 4 years.

Pertussis-containing Vaccine Characteristics

- Administered by intramuscular injection
- Contains aluminum as an adjuvant

Characteristics

Pertussis vaccines are administered by intramuscular injection. Each dose of pertussis-containing vaccine contains aluminum as an adjuvant but no preservative. DTaP-HepB-IPV (Pediarix), DTaP-IPV/Hib (Pentacel), DTaP-IPV-Hib-HepB (Vaxelis), DTaP-IPV (Kinrix), and DTaP-IPV (Quadracel) contain neomycin and polymyxin B as antibiotics. DTaP-IPV-Hib-HepB (Vaxelis) contains streptomycin as an antibiotic. DTaP-HepB-IPV (Pediarix) and DTaP-IPV-Hib-HepB (Vaxelis) vaccines contain yeast protein. Presentations of some pertussis-containing vaccines contain latex rubber.

Pertussis-containing Vaccination Schedule

- DTaP
  - 3-dose primary series at age 2, 4, and 6 months
  - Primary series interval of 4- to 8-weeks and minimum interval 4 weeks
  - Boosters at age 15 through 18 months and age 4 through 6 years
  - Minimum interval for dose 4 is 6 months from dose 3 and minimum age is 12 months
  - If dose 4 is given on or after 4th birthday, the 5th dose is optional
  - DT is used in place of DTaP if child has a valid contraindication to pertussis vaccine

Vaccination Schedule and Use

DTaP (Infanrix and Daptacel)

DTaP (diphtheria, tetanus toxoids, and acellular pertussis vaccine) is recommended for children age 6 weeks through 6 years. The routine schedule is a primary series of 3 doses at age 2, 4, and 6 months, a booster dose between age 15 through 18 months, and another booster dose between age 4 through 6 years (total of 5 doses). The first 3 doses should be given at 4- to 8-week intervals (minimum of 4 weeks). Dose 4 should follow dose 3 by no less than 6 months and should not be administered before age 12 months.

Dose 4 of both brands of DTaP is recommended to be administered at age 15 through 18 months (15 through 20 months for Daptacel). Dose 4 may be given as early as age 12 months if at least 6 months have elapsed since dose 3 and, in the opinion of the vaccine provider, the child is unlikely to return for an additional visit between age 15 through 18 months.

Children who received 4 doses before their fourth birthday should receive a fifth dose of DTaP before entering school. The fifth dose is not necessary (but may be given) if dose 4 in the series was given on or after the fourth birthday. Administering the fifth dose increases antibody levels and may decrease the risk of school-age children transmitting the disease to younger siblings who are not fully vaccinated.

If a child has a valid contraindication to pertussis vaccine, DT should be used to complete the vaccination series. If the child was younger than age 12 months when the first dose of DT was administered (as DTP, DTaP, or DT), the child should receive a total of 4 DT doses. If the child was age 12 months or older at the time the first dose of DT was administered, 3 doses

(with dose 3 administered 6 through 12 months after dose 2) will complete the primary DT series. If dose 4 of DTP, DTaP, or DT is administered before the fourth birthday, a fifth dose is recommended at age 4 through 6 years.

DTaP-HepB-IPV (Pediarix)

DTaP-HepB-IPV vaccine is approved for use as a 3-dose series for children age 6 weeks through 6 years. It is administered to infants at age 2, 4, and 6 months. The minimum intervals for DTaP-HepB-IPV vaccine are determined by the DTaP component. The 3 doses must be separated by at least 4 weeks between doses. Because the minimum age for the first dose of DTaP-HepB-IPV vaccine is 6 weeks, this vaccine cannot be used for the birth dose of hepatitis B (HepB) vaccine. The final dose of DTaP-HepB-IPV vaccine should be administered at age 24 weeks or older, the minimum age for completion of the hepatitis B vaccine series. When DTaP-HepB-IPV vaccine is used to provide 3 doses at age 2, 4, and 6 months (based on the DTaP and IPV schedules), this will result in a 4-dose HepB vaccine series, which is acceptable.

DTaP-IPV/Hib (Pentacel)

DTaP-IPV/Hib vaccine is approved for use as a 4-dose series for children age 6 weeks through 4 years. It is administered to infants at age 2, 4, 6, and 15 through 18 months. The minimum intervals for DTaP-IPV/Hib vaccine are determined by the DTaP component. The first 3 doses must be separated by at least 4 weeks between doses. Dose 4 must be separated from dose 3 by at least 6 months, and should not be administered before age 12 months. When DTaP-IPV/Hib vaccine is used to provide 4 doses at age 2, 4, 6, and between 15 through 18 months (based on the DTaP and Hib schedules), an additional booster dose with IPV-stand alone or DTaP-IPV vaccine should be administered at age 4 through 6 years. This will result in a 5-dose IPV vaccine series, which is acceptable.

DTaP-IPV-Hib-HepB (Vaxelis)

DTaP-IPV-Hib-HepB is approved for use as a 3-dose series for children age 6 weeks through 4 years. It is administered to infants at age 2, 4, and 6 months. The minimum intervals for DTaP-IPV-Hib-HepB vaccine are determined by the DTaP component. The 3 doses must be separated by at least 4 weeks between doses. Because the minimum age for the first dose of DTaP-IPV-Hib-HepB vaccine is 6 weeks, this vaccine cannot be used for the birth dose of hepatitis B (HepB) vaccine. The final dose of DTaP-IPV-Hib-HepB vaccine should be administered at age 24 weeks or older, the minimum age for completion of the hepatitis B vaccine series. When DTaP-IPV-Hib-HepB vaccine is used to provide 3 doses at age 2, 4, and 6 months (based on the DTaP and IPV schedules), this will result in a 4-dose HepB vaccine series, which is acceptable.

DTaP-IPV (Kinrix)

DTaP-IPV (Kinrix) vaccine is approved only for dose 5 of DTaP vaccine and dose 4 of IPV vaccine in children age 4 through 6 years whose previous DTaP vaccine doses have been with Infanrix and/or Pediarix for dose 1, 2, and 3 and Infanrix for dose 4. However, if DTaP-IPV (Kinrix) vaccine is administered to children who received another brand of DTaP vaccine for prior DTaP vaccine doses, or if administered as dose 1, 2, 3, or 4 of the DTaP vaccine series or dose 1, 2, or 3 of the IPV vaccine series, the dose of DTaP-IPV (Kinrix) does not need to be repeated.

DTaP-IPV (Quadracel)

DTaP-IPV (Quadracel) vaccine is approved only for dose 5 of DTaP vaccine and dose 4 or 5 of IPV vaccine in children age 4 through 6 years who have received 4 doses of Pentacel and/or Daptacel vaccine. However, if DTaP-IPV (Quadracel) vaccine is administered to children who received another brand of DTaP vaccine for prior DTaP vaccines doses, or if administered as dose 1, 2, 3, or 4 of the DTaP vaccine series or dose 1, 2, or 3 of the IPV series, the dose of DTaP-IPV (Quadracel) does not need to be repeated.

Pertussis-containing Vaccination Schedule

- Tdap
  - 1 dose at age 11 through 18 for adolescents who have completed DTaP series
  - Booster dose of Td or Tdap every 10 years for all persons

Tdap (Boostrix and Adacel) and Td (Tenivac and Tdvax)

Both Tdap vaccines are approved by the FDA for a booster dose for persons who have completed the recommended childhood DTP/DTaP vaccination series. Boostrix is approved for persons age 10 years or older. Adacel is approved for a single dose in persons age 10 through 64 years. A second dose of Adacel is also licensed for administration 8 or more years after the first Tdap dose and for use for tetanus prophylaxis when indicated for wound management if at least 5 years have elapsed since the previous receipt of any tetanus toxoid-containing vaccine.

A single Tdap dose is recommended for adolescents age 11 through 18 years who have completed the recommended childhood DTP/DTaP vaccination series, preferably at age 11 through 12 years. Adults age 19 years or older who have not previously received Tdap should receive a single dose of Tdap. To reduce the burden of pertussis in infants, a dose of Tdap has been recommended during each pregnancy since 2012, although this practice is an off-label use.

All adolescents and adults should have received a primary series of at least 3 documented doses of tetanus and diphtheria toxoids-containing vaccine (i.e., DTaP, DTP, DT, or Td) during their lifetime. A person without such documentation should receive a series of 3 doses of tetanus- and diphtheria-containing vaccine. One of these doses, preferably the first, should be Tdap. The remaining 2 doses should be either Td or Tdap.

For persons age 7 to 9 years who receive a dose of Tdap as part of the catch-up series, an adolescent Tdap dose should be administered at age 11 through 12 years. If a Tdap dose is administered at age 10 years or older, the Tdap dose may count as the adolescent Tdap dose. Either brand of Tdap may be used.

Adults age 19 years or older who previously have not received Tdap should receive a single dose of Tdap to protect against pertussis and reduce the likelihood of transmission. For adults age 19 through 64 years, either brand of Tdap may be used. Adults age 65 years or older should be vaccinated with Boostrix, if feasible. However, either vaccine administered to a person age 65 years or older is immunogenic and would provide protection. A dose of either vaccine would be considered valid.

Adolescents and adults who have not previously received Tdap, and have or anticipate having close contact with an infant younger than age 12 months (e.g., parents, siblings, grandparents, child care providers, and health care personnel) should receive a single dose of Tdap to protect against pertussis. Ideally, these persons should receive Tdap at least 2 weeks before beginning close contact with the infant.

Health care personnel should receive a single dose of Tdap as soon as feasible if they have not previously received Tdap, regardless of the time since their most recent Td vaccination.

When Tdap is indicated (e.g., routine vaccination, catch-up vaccination, or pregnancy), it can be administered regardless of the interval since the last tetanus- or diphtheria-toxoid-containing vaccine. After receipt of Tdap, persons should continue to receive a dose of Td or Tdap for routine booster immunization against tetanus and diphtheria every 10 years unless needed sooner for tetanus prophylaxis as part of wound management.

Use of Tdap

- 1 dose Tdap during each pregnancy (off-label use)
- 1 dose Tdap for the following with no previous documentation of Tdap: adults, adolescents and adults who have or anticipate having close contact with an infant younger than age 12 months, and health care personnel
- 3 doses of tetanus- and diphtheria-containing vaccine (1 dose should be Tdap) for adolescents and adults without documentation of a primary series

Vaccination during Pregnancy

To reduce the burden of pertussis in infants, health care providers should administer a dose of Tdap during each pregnancy, regardless of the mother's prior Tdap vaccination history, although this is an off-label use. To maximize the maternal antibody response and passive antibody transfer to the infant, optimal timing for Tdap administration is between 27 and 36 weeks of gestation, preferably during the earlier part of this period, although Tdap may be administered at any time during pregnancy. For women not previously vaccinated with Tdap, if Tdap is not administered during pregnancy, Tdap should be administered immediately postpartum. Tdap should be administered during each pregnancy (preferred) or during the postpartum period regardless of the interval since the last tetanus- or diphtheria toxoid-containing vaccine.

Pertussis-containing Vaccine Efficacy

- DTaP vaccine efficacy 80%-85%
- Tdap similar efficacy

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 DTaP vaccine efficacy ranged from 80% to 85%, with overlapping confidence intervals.

Adolescent and adult formulation Tdap vaccines were licensed on the basis of noninferiority of the serologic response to the various components compared with each company's pediatric DTaP formulation among persons who had received pediatric DTaP or DTP in childhood. For both vaccines, the antibody response to a single dose of Tdap was similar to that following 3 doses of DTaP in infants. This type of study is known as "bridging." The new vaccines are assumed to have similar clinical efficacy as DTaP vaccine since a similar level of antibody to the components was achieved.

Studies on the persistence of antipertussis antibodies following a dose of Tdap show antibody levels in healthy, nonpregnant adults peak during the first month after vaccination, with antibody levels declining after 1 year. Because antibody levels wane substantially during the first year after vaccination, ACIP concluded a single dose of Tdap during one pregnancy would not be sufficient to provide protection for subsequent pregnancies.

Pertussis-containing Vaccine Contraindications and Precautions

- Contraindication
  - Severe allergic reaction to vaccine component or following a prior dose
  - Encephalopathy not attributable to another identifiable cause within 7 days after vaccination*
- Precaution
  - Moderate or severe acute illness
  - Progressive or unstable neurological disorder*
  - Uncontrolled seizures*
  - Progressive encephalopathy*
  - Guillain-Barré syndrome within 6 weeks after a previous dose of tetanus-toxoid containing vaccine**
  - History of Arthus-type hypersensitivity reactions after a previous dose of diphtheria toxoid- or tetanus toxoid-containing vaccine**

*DTaP and Tdap

**DTaP, DT, Tdap, Td

Contraindications and Precautions to Vaccination

As with other vaccines, a history of a severe allergic reaction (anaphylaxis) to a vaccine component or following a prior dose is a contraindication to further doses. Moderate or severe acute illness (with or without fever) in a patient is considered a precaution to vaccination, although persons with minor illness may be vaccinated.

Contraindications to combination vaccines that contain DTaP include the contraindications to the individual component vaccines (e.g., IPV, hepatitis B, Hib), but specific ingredients might differ. DTaP-HepB-IPV (Pediarix) and DTaP-IPV-Hib-HepB (Vaxelis) vaccines contain yeast. Presentations of some pertussis-containing vaccines contain latex rubber. DTaP-HepB-IPV (Pediarix), DTaP-IPV/Hib (Pentacel), DTaP-IPV-Hib-HepB (Vaxelis), DTaP-IPV (Kinrix), and DTaP-IPV (Quadracel) contain neomycin and polymyxin B. DTaP-IPV-Hib-HepB (Vaxelis) contains streptomycin.

Encephalopathy not attributable to another identifiable cause occurring within 7 days after vaccination with DTaP, DTP, or Tdap is a contraindication for DTaP and Tdap vaccination.

A progressive or unstable neurological disorder, uncontrolled seizures, or progressive encephalopathy is a precaution for DTaP and Tdap vaccination. For persons with a known or suspected neurologic condition, vaccination with DTaP or Tdap should be delayed until the condition has been evaluated, treatment initiated, and the condition stabilized. These conditions include the presence of an evolving neurologic disorder (e.g., uncontrolled epilepsy, infantile spasms, and progressive encephalopathy); a history of seizures that has not been evaluated; or a neurologic event that occurs between doses of 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 neither contraindications nor precautions to DTaP or Tdap vaccination.

Guillain-Barré syndrome within 6 weeks after a previous dose of tetanus toxoid-containing vaccine is a precaution for DTaP, Tdap, DT, and Td vaccination.

A history of Arthus-type hypersensitivity reactions after a previous dose of diphtheria toxoid-containing or tetanus toxoid-containing vaccine is a precaution for DTaP, Tdap, DT, and Td vaccination; vaccination should be deferred until at least 10 years have elapsed since the last tetanus toxoid-containing vaccine.

Vaccine Safety

DTaP vaccine may cause local reactions, such as pain, redness, or swelling. Local reactions have been reported in 20% to 40% of children after each of the first 3 doses. Local reactions appear to be more frequent after the fourth and/or fifth doses. Mild systemic reactions such as drowsiness, fretfulness, and low-grade fever may also occur. Temperature of 101°F or higher is reported in 3% to 5% of DTaP recipients. These reactions are self-limited and can be managed with symptomatic treatment with acetaminophen or ibuprofen.

Moderate or severe systemic reactions (such as fever of 105°F or higher, febrile seizures, persistent crying lasting 3 hours or longer, and hypotonic-hyporesponsive episodes) have been reported after administration of DTaP, but occur less frequently than among children who received whole-cell DTP. Rates of these moderate or severe systemic reactions vary by symptom and vaccine but generally occur in fewer than 1 in 10,000 doses.

Exaggerated local (Arthus-type) reactions are rarely reported but may occur following receipt of a vaccine containing diphtheria or tetanus toxoids.

The most common adverse reaction following vaccination with both brands of Tdap is a local reaction, such as pain (66% to 75%), redness (25%), or swelling (21%) at the site of injection.

Pertussis-containing Vaccine Safety

DTaP

- Pain, redness, or swelling
  - 20%-40%
- Temperature of 101°F
  - 3%-5%
- Moderate or severe systemic reactions
  - Fewer than 1 in 10,000 doses
- Arthus-type reactions are rare

Tdap, Td

- Pain, redness, or swelling
  - 21%-75%
- Temperature of 100.4°F or higher
  - 1.1%-5%

Temperature of 100.4°F or higher was reported by 1.4% to 5% of Tdap recipients and 1.1% to 5% of Td recipients. Tdap recipients also reported a variety of nonspecific systemic events, such as headache, fatigue and gastrointestinal symptoms.

The Institute of Medicine reported in 2011 that the evidence was inadequate to accept or reject a causal relation between receipt of diphtheria toxoid and tetanus toxoid-containing vaccine and encephalitis, encephalopathy, infantile spasms, seizures, ataxia, autism, acute disseminated encephalomyelitis, transverse myelitis, optic neuritis, onset of multiple sclerosis in adults, relapse of multiple sclerosis in adults, relapse of multiple sclerosis in children, Guillain-Barré syndrome, chronic inflammatory disseminated polyneuropathy, opsoclonus myoclonus syndrome, or Bell's palsy.

The most frequently reported adverse events after DTaP in the Vaccine Adverse Effect Reporting System (VAERS) and Vaccine Safety Datalink (VSD), two post-licensure surveillance systems, were consistent with observations from pre-licensure studies of these vaccines. When VAERS DTaP reports for each vaccine brand were compared individually with reports for all other inactivated vaccines in the VAERS database, no concerning patterns of adverse events were observed.

Routine VAERS surveillance for and VSD studies on adverse events following receipt of Tdap vaccines in persons aged 10 through 64 years have provided reassuring data consistent with the prelicensure clinical trial safety data and have not demonstrated any associations between Tdap and the following rare adverse events: encephalopathy-encephalitis-meningitis, paralytic syndromes, seizures, cranial nerve disorders, and Guillain-Barré syndrome.

Vaccine Storage and Handling

DTaP and Tdap vaccines should be maintained at refrigerator temperature between 2°C and 8°C (36°F and 46°F). Manufacturer package inserts contain additional information. For complete information on best practices and recommendations, please refer to CDC's Vaccine Storage and Handling Toolkit, www.cdc.gov/vaccines/hcp/admin/storage/toolkit/storage-handling-toolkit.pdf.

Surveillance and Reporting of Pertussis

For information on guidance for state and local health department staff who are involved in surveillance activities for vaccine-preventable diseases, please consult the Manual for the Surveillance of Vaccine-Preventable Diseases, www.cdc.gov/vaccines/pubs/surv-manual/chapters.html

Acknowledgements

The editors would like to acknowledge Jennifer Liang, Stacey Martin, and Cindy Weinbaum for their contributions to this chapter.

Selected References

American Academy of Pediatrics. Pertussis. In: Kimberlin D, Brady M, Jackson M, et al., eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics;2018:620–34.

CDC. Prevention of pertussis, tetanus, and diphtheria with vaccines in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2018;67(RR-2):1–44.

CDC. Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Tdap) in pregnant women and persons who have or anticipate having close contact with an infant <12 months of age – Advisory Committee on Immunization Practices (ACIP). *MMWR* 2011;60(41):1424–6.

CDC. Use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccines: updated recommendations of the Advisory Committee on Immunization Practices — United States, 2019. *MMWR* 2020;69(3):77–83.

Cherry J, The epidemiology of pertussis: a comparison of the epidemiology of the disease pertussis with the epidemiology of *Bordetella pertussis* infection. *Pediatrics* 2005;115(5):1422–7.

Edwards K, Decker M. Pertussis Vaccines. In: Plotkin S, Orenstein W, Offit P, et al., eds. Plotkin's *Vaccines*. 7th ed. Elsevier;2018:711–61.

Elam-Evans L, Yankey D, Singleton J, et al. National, Regional, State, and Selected Local Area Vaccination Coverage Among Adolescents Aged 13–17 Years — United States, 2019. *MMWR* 2020;69(33):1109–16.

Greenberg D. Pertussis in adolescents: increasing incidence brings attention to the need for booster immunization of adolescents. *Pediatr Infect Dis* J 2005;24(8):721–8.

Skoff T, Hadler S, Hariri S. The epidemiology of nationally reported pertussis in the United States, 2000–2016. *Clin Infect Dis* 2019 68(10):1634–40.

NOTES

NOTES

Skoff T, Kenyon C, Cocoros N, et al. Sources of infant pertussis infection in the United States. *Pediatrics* 2015;136(4):635–41.

Ward J, Cherry J, Chang S, et al. Efficacy of an acellular pertussis vaccine among adolescents and adults. *N Engl J Med* 2005;353:1555–63.

Woo E, Burwen D, Gatumu SN, et al. Extensive limb swelling after immunization: Reports to the Vaccine Adverse Event Reporting System. *Clin Infect Dis* 2003;37(3):351–8.

Yeung K, Duclos P, Nelson E, et al. An update of the global burden of pertussis in children younger than 5 years: a modelling study. *Lancet Infect Dis.* 2017;17(9):974–80.

Pneumococcal Disease

Ryan Gierke, MPH; A. Patricia Wodi, MD; and Miwako Kobayashi, MD, MPH

Streptococcus pneumoniae causes acute bacterial infections. The bacterium, also called pneumococcus, was first isolated by Louis Pasteur in 1881 from the saliva of a patient with rabies. The association between pneumococcus and lobar pneumonia was first described in 1883, but pneumococcal pneumonia was confused with other types of pneumonia until the development of the Gram stain in 1884. Between 1915 and 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 described. More than 80 serotypes of pneumococci had been described by 1940.

Efforts to develop effective pneumococcal vaccines began as early as 1911. However, with the advent of penicillin in the 1940s, interest in pneumococcal vaccination 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 for use in the United States in 1977. The first conjugate pneumococcal vaccine was licensed in the United States in 2000.

Pneumococcal Disease

- *S. pneumoniae* first isolated by Pasteur in 1881
- Confused with other types of pneumonia until discovery of Gram stain in 1884
- More than 80 serotypes described by 1940
- First pneumococcal vaccine licensed in U.S. in 1977; first conjugate pneumococcal vaccine in 2000

Streptococcus pneumoniae

S. pneumoniae bacteria are lancet-shaped, gram-positive, facultative anaerobic organisms. They are typically observed in pairs (diplococci) but may also occur singularly or in short chains. Most pneumococci are encapsulated, and their surfaces are composed of complex polysaccharides. Capsular polysaccharides are one determinant of the pathogenicity of the organism. They are also antigenic and form the basis for classifying pneumococci by serotypes. One hundred serotypes were documented as of 2020, based on their reaction with type-specific antisera. Type-specific antibody to capsular polysaccharide is protective against disease caused by that serotype. These antibodies and complement interact to opsonize pneumococci, which facilitates phagocytosis and clearance of the organism. Antibodies to some pneumococcal capsular polysaccharides may cross-react with related types as well as with other bacteria, providing protection against additional serotypes.

Most *S. pneumoniae* serotypes have been shown to cause serious disease, but only a few serotypes cause most pneumococcal infections. The ranking and serotype prevalence differ by patient age group and geographic area. In the United States, prior to the widespread use of 7-valent pneumococcal conjugate vaccine (PCV7), the seven most common serotypes isolated from blood or cerebrospinal fluid (CSF) of children

Streptococcus pneumonia

- Facultative anaerobic gram-positive organism
- 100 serotypes documented as of 2020
- Most serotypes cause serious disease, only a few cause most pneumococcal infections
- Serotype prevalence differ by age and geographic area

younger than age 5 years accounted for 80% of infections; these seven serotypes accounted for about 50% of isolates from older children and adults.

The clinical spectrum of pneumococcal infections ranges from invasive disease (i.e., infection of normally sterile sites including osteomyelitis, bacteremia without focus of infection, pneumonia with bacteremia, septic arthritis, and meningitis) to non-invasive infections such as pneumonia without bacteremia, otitis media, and sinusitis. Pneumococci cause more than 50% of all cases of bacterial meningitis in the United States with approximately 2,000 cases of pneumococcal meningitis occurring each year. Over 150,000 hospitalizations from pneumococcal pneumonia are estimated to occur annually in the United States and it has been demonstrated to complicate influenza infection. Pneumococci is the most common bacterial cause of childhood pneumonia, especially in children younger than age 5 years. In adults, pneumococci account for 10% to 30% of adult community-acquired pneumonia.

Pneumococcal Disease Pathogenesis

- Pneumococci commonly inhabit respiratory tract
- Asymptomatic carriage varies
  - School-age children 20% to 60%
  - Adults 5% to 10%
- Relationship of carriage to development of natural immunity is poorly understood

Pathogenesis

Pneumococci are common inhabitants of the respiratory tract and may be isolated from the nasopharynx of 5% to 90% of healthy persons. Rates of asymptomatic carriage vary with age, environment, and the presence of upper respiratory infections. Among school-age children, 20% to 60% may be colonized. Only 5% to 10% of adults without children are colonized, although on military installations, as many as 50% to 60% of service personnel may be colonized. The duration of carriage varies and is generally longer in children than adults. The relationship of carriage to the development of natural immunity is poorly understood.

Pneumococcal Disease Clinical Features

- Major clinical syndromes are pneumonia, bacteremia, and meningitis

Clinical Features

The major clinical syndromes of invasive pneumococcal disease are pneumonia, bacteremia, and meningitis.

Pneumococcal Disease in Adults

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 a single rigor. Repeated shaking chills are uncommon. Other common symptoms include pleuritic chest pain, cough productive of mucopurulent, rusty sputum, dyspnea, tachypnea, hypoxia, tachycardia, malaise, and weakness. Nausea, vomiting, and headaches occur less frequently. Complications of pneumococcal pneumonia include bacteremia, empyema (i.e., infection of the pleural space), pericarditis (inflammation of the sac surrounding the heart), and

endobronchial obstruction, with atelectasis (partial collapse of lung tissue) and lung abscess formation.

Pneumococcal bacteremia can occur with or without pneumonia and lead to arthritis, meningitis, and endocarditis. The case fatality ratio of pneumonia with bacteremia is around 10%. More than 5,000 cases of pneumococcal bacteremia without pneumonia occur each year. The overall case fatality ratio for bacteremia is about 12%. Patients with asplenia who develop bacteremia may experience a fulminant clinical course.

Some patients with pneumococcal meningitis also have pneumonia. The clinical symptoms, CSF profile, and neurologic complications of pneumococcal meningitis are similar to other forms of purulent bacterial meningitis. Symptoms may include headache, lethargy, vomiting, irritability, fever, nuchal rigidity, cranial nerve signs, seizures, and coma. The case fatality ratio of pneumococcal meningitis is about 14% among adults. Neurologic sequelae are common among survivors.

Adults with certain medical conditions are at highest risk for invasive pneumococcal disease. For adults age 18 through 64 years with hematologic cancer, the rate of invasive pneumococcal disease in 2013–2014 was 129 per 100,000 population. Other conditions that place adults at highest risk for invasive pneumococcal disease include other immunosuppressive conditions from disease or drugs, functional or anatomic asplenia, and renal disease. Other conditions that increase the risk of invasive pneumococcal disease in adults include chronic heart disease, lung disease (including asthma), liver disease, smoking cigarettes, alcoholism, CSF leak, and having a cochlear implant.

Pneumococcal Disease in Adults

- Pneumococcal pneumonia
  - Most common clinical presentation
  - Incubation period 1 to 3 days
  - Symptoms: Fever, chills, pleuritic chest pain, cough, rusty sputum, dyspnea, tachypnea, hypoxia, tachycardia, malaise, weakness
- Pneumococcal bacteremia
  - Can lead to arthritis, meningitis, and endocarditis
  - 12% overall case fatality ratio
- Pneumococcal meningitis
  - Symptoms: Headache, lethargy, vomiting, irritability, fever, nuchal rigidity, cranial nerve signs, seizures, coma
  - 14% case fatality ratio

Pneumococcal Disease in Children

Bacteremia without a known site of infection is the most common invasive clinical presentation of pneumococcal infection among children age 2 years or younger, accounting for approximately 40% of invasive disease in this age group. Bacteremic pneumonia accounts for 25% to 30% of invasive pneumococcal disease among children age 2 years or younger. With the decline of invasive *Haemophilus influenzae* type b (Hib) disease, *S. pneumoniae* has become the leading cause of bacterial meningitis among children younger than age 5 years in the United States. Before routine use of pneumococcal conjugate vaccine, children younger than 1 year had the highest rates of pneumococcal meningitis, approximately 10 cases per 100,000 population.

Pneumococci are a common cause of acute otitis media and are detected in 24% to 31% of middle ear aspirates. By age 12 months, more than 60% of children have had at least one episode of acute otitis media. Middle ear infections

Pneumococcal Disease in Children

- Pneumococcal pneumonia
  - Accounts for 25% to 30% of invasive disease in children age 2 years or younger
- Pneumococcal bacteremia
  - Accounts for 40% of invasive disease in children age 2 years or younger
- Pneumococcal meningitis
  - *S. pneumoniae* leading cause of bacterial meningitis among children younger than age 5 years
- Pneumococci common cause of acute otitis media

are a leading reason for pediatric office visits in the United States, resulting in more than 10 million visits annually. Complications of pneumococcal otitis media may include mastoiditis and meningitis.

Children with functional or anatomic asplenia, particularly those with sickle cell disease, and children with immunocompromising conditions are at very high risk for invasive disease, with rates in some studies more than 50 times higher than those among children of the same age without these conditions (i.e., incidence rates of 5,000 to 9,000 per 100,000 population). Other conditions that increase the risk of invasive pneumococcal disease in children include chronic heart disease, lung disease (including asthma if treated with high-dose oral corticosteroid therapy), liver disease, CSF leak, and having a cochlear implant. Rates are also increased among children of certain racial and ethnic groups, including Alaska Natives, African Americans, and certain American Indian groups (Navajo and White Mountain Apache). The reason for this increased risk by race and ethnicity is not known with certainty but has also been noted for invasive *Haemophilus influenzae* infection (also an encapsulated bacterium). Attendance at a childcare center has also been shown to increase the risk of invasive pneumococcal disease and acute otitis media 2- or 3-fold among children younger than age 5 years. Children with a cochlear implant are at increased risk for pneumococcal meningitis.

Laboratory Testing

A definitive diagnosis of infection with *S. pneumoniae* generally relies on isolation of the organism from blood or other normally sterile body sites (e.g., CSF, middle ear fluid, joint fluid, and peritoneal fluid). 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 sputum includes more than 25 white blood cells and fewer than 10 epithelial cells per low-power field, and a predominance of gram-positive diplococci.

A urinary antigen test based on an immunochromatographic membrane technique to detect the C-polysaccharide antigen of *S. pneumoniae* as a cause of community-acquired pneumonia among adults is commercially available and has been cleared by FDA. The test is rapid and simple to use, has a reasonable specificity in adults, and has the ability to detect pneumococcal pneumonia after antibiotic therapy has been started.

Antimicrobial Resistance

S. pneumoniae resistance to penicillin and other antibiotics was previously very common. Following introduction of PCV7, antibiotic resistance declined and then began to increase again. Then, in 2008, the definition of penicillin resistance was changed such that a much larger proportion of pneumococci were considered susceptible to penicillin. The revised susceptibility breakpoints for *S. pneumoniae*, published by the Clinical and Laboratory Standards Institute (CLSI) in January 2008, were the result of a reevaluation that showed clinical response to penicillin was being preserved in clinical studies of pneumococcal infection, despite reduced susceptibility response in vitro. Since introduction of 13-valent pneumococcal conjugate vaccine (PCV13) in children in 2010, antibiotic-resistant pneumococcal infections declined significantly.

Epidemiology

Occurrence

Pneumococcal disease occurs throughout the world.

Reservoir

S. pneumoniae is a human pathogen. The reservoir for pneumococci is the nasopharynx of asymptomatic humans. There is no animal or insect vector.

Transmission

Transmission of *S. pneumoniae* occurs as the result of direct person-to-person contact via respiratory droplets or by autoinoculation in persons carrying the bacteria in their upper respiratory tract. Different pneumococcal serotypes have different propensities for causing asymptomatic colonization, otitis media, meningitis, and pneumonia. The spread of the organism within a family or household is influenced by such factors as household crowding and viral respiratory infections.

Temporal Pattern

Pneumococcal infections are more common during the winter and in early spring when respiratory diseases are more prevalent.

Communicability

The period of communicability for pneumococcal disease is unknown, but presumably transmission can occur as long as the organism appears in respiratory secretions.

Pneumococcal Disease Epidemiology

- Reservoir
  - Humans
- Transmission
  - Person-to-person through respiratory droplets or by autoinoculation
- Temporal pattern
  - More common during winter and early spring
- Communicability
  - Presumably transmissible as long as organism is in respiratory secretions

Pneumococcal Disease Secular Trends in the United States

- In 2017, more than 31,000 cases and 3,500 deaths from invasive pneumococcal disease; more than 50% occurred in adults
- Before routine use of pneumococcal conjugate vaccine, annual burden in children younger than age 5 years was significant:
  - 17,000 cases of invasive disease
  - 200 deaths from invasive pneumococcal disease
  - 5 million cases of acute otitis media
- Since use of pneumococcal conjugate vaccine in children, invasive disease caused by serotypes in PCV7 declined 99% in children
- Since introduction of PCV13, invasive disease caused by PCV13 serotypes declined 90% in children

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 31,000 cases and more than 3,500 deaths from invasive pneumococcal disease (bacteremia and meningitis) are estimated to have occurred in the United States in 2017. More than half of these cases occurred in adults who had an indication for pneumococcal polysaccharide vaccine.

Before routine use of pneumococcal conjugate vaccine in 2000, the burden of pneumococcal disease among children younger than age 5 years was significant. An estimated 17,000 cases of invasive disease occurred each year, of which 13,000 were bacteremia without a known site of infection and about 700 were meningitis. An estimated 200 children died every year as a result of invasive pneumococcal disease. Although not considered invasive disease, an estimated 5 million cases of acute otitis media occurred each year among children younger than 5 years of age. The widespread use of pneumococcal conjugate vaccines in children has resulted in a decrease in transmission of vaccine-type strains, thereby preventing pneumococcal disease among unvaccinated children and adults.

Data from the Active Bacterial Core surveillance (ABCs) system indicate that in 2008, before PCV13 replaced PCV7 for routine use among children, approximately 61% of invasive pneumococcal disease cases among children younger than age 5 years were attributable to the serotypes included in PCV13, with serotype 19A accounting for 43% of cases; PCV7 serotypes caused less than 2% of cases.

ABCs data suggest that the use of pneumococcal conjugate vaccine has had a major impact on the incidence of invasive disease among young children. The reductions in overall incidence resulted from a 99% decrease in disease caused by the seven serotypes in PCV7 and serotype 6A, a serotype against which PCV7 provides some cross-protection. The decreases were offset partially by increases in invasive disease caused by serotypes not included in PCV7, in particular 19A. In 2010, PCV13 replaced PCV7 in the United States. PCV13 contains the serotypes in PCV7, plus 6 additional serotypes, including 19A. Since PCV13 introduction, invasive disease caused by PCV13 serotypes has declined 90% in children. Declines have been sustained and have not been offset by increases in non-vaccine type disease.

Among children born during 2016–2017, 91.6% had received at least 3 doses of PCV, and 81.7% had received at least 4 doses, by age 24 months. In 2017, 69.0% of persons age 65 years or older had ever received a pneumococcal vaccine. Vaccination coverage levels in 2017 were 24.5% among persons age 19 through 64 years at increased risk for pneumococcal disease.

Opportunities to vaccinate persons at increased risk of pneumococcal disease are missed both at the time of hospital discharge and during visits to clinicians' offices. Effective programs for vaccine delivery are needed, including offering the vaccine in hospitals at discharge and in clinicians' offices, nursing homes, and other long-term care facilities.

More than 65% of persons hospitalized with severe pneumococcal disease had been admitted to a hospital in the preceding 3 to 5 years, yet few had received pneumococcal vaccine. In addition, persons who frequently visit physicians and who have chronic conditions are more likely to be at increased risk of pneumococcal infection than those who require infrequent visits. Screening and subsequent immunization of hospitalized persons found to be at increased risk could have a significant impact on reducing complications and death associated with pneumococcal disease.

Pneumococcal Vaccines

The first pneumococcal polysaccharide vaccine was licensed for use in the United States in 1977. It contained purified capsular polysaccharide antigen from 14 different types of pneumococci. In 1983, a 23-valent polysaccharide vaccine (PPSV23, Pneumovax 23) was licensed and replaced the 14-valent vaccine, which is no longer produced.

Pneumococcal Vaccines

- PPSV23 (Pneumovax 23)
- PCV13 (Prevnar 13)

The first pneumococcal conjugate vaccine (Prevnar 7, PCV7) was licensed for use in the United States in 2000. It included purified capsular polysaccharide of seven serotypes of *S. pneumoniae*. In 2010, a 13-valent pneumococcal conjugate vaccine (PCV13, Prevnar 13) was licensed in the United States. It contains the same 7 serotypes of *S. pneumoniae* as PCV7 plus serotypes 1, 3, 5, 6A, 7F, and 19A.

In 2008, the serotypes covered in PCV13 caused 53%, 49%, and 44% of invasive pneumococcal disease cases among persons age 18 through 49 years, 50 through 64 years, and 65 years or older, respectively; serotypes covered in PPSV23 caused 78%, 76%, and 66% of IPD cases among persons in these age groups.

Characteristics

Pneumococcal Polysaccharide Vaccine

PPSV23 is composed of purified preparations of pneumococcal capsular polysaccharide from 23 types of pneumococci. The serotypes are: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F. PPSV23 is administered by either intramuscular or subcutaneous injection. Each dose of PPSV23 contains phenol as a preservative. It contains no adjuvant or antibiotic.

Pneumococcal Vaccine Characteristics

- PPSV23
  - Administered by intramuscular or subcutaneous injection
  - Contains phenol as a preservative
- PCV13
  - Administered by intramuscular injection
  - Contains aluminum phosphate as an adjuvant

Pneumococcal Conjugate Vaccine

PCV13 contains 13 serotypes of *S. pneumoniae* (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) conjugated to a nontoxic variant of diphtheria toxin known as CRM197. PCV13 is administered by intramuscular injection. Each dose of PCV13 contains aluminum phosphate as an adjuvant. It contains no antibiotic or preservative.

Pneumococcal Vaccination Schedule

- PCV13
  - 3-dose primary series at age 2, 4, and 6 months
  - Booster at age 12 through 15 months
  - Minimum age for dose 1 is 6 weeks
  - Minimum interval for doses before age 1 year is 4 weeks and age 1 year or older is 8 weeks
  - Unvaccinated children age 7 months or older require fewer doses
  - Shared clinical decision making for age 65 years or older
- PPSV23
  - 1 dose for all adults age 65 years or older
- Schedule for PCV13 and PPSV23 varies by medical condition

Vaccination Schedule and Use

All children age 2 through 59 months should routinely receive PCV13, and all adults age 65 years or older should receive PPSV23. In addition, persons age 2 years or older with certain conditions (see table "Conditions with Pneumococcal Vaccination Indications" below) should receive both PCV13 and PPSV23, or PPSV23 alone. PPSV23 is not recommended for children younger than age 2 years. Children and adults who have a condition for which PCV13 is indicated should receive PCV13 first, followed by PPSV23 at least 8 weeks later. Adults age 65 years or older, who do not have any conditions for PCV13 indication (see table "Conditions with Pneumococcal Vaccination Indications" below), can discuss with their clinician and decide whether to receive PCV13 (shared clinical decision making). If the decision is made to receive PCV13 based on shared clinical decision making, it should be given at least 1 year before PPSV23.

Conditions with Pneumococcal Vaccination Indications

Conditions	PCV13 indicated for 2 through 71 Months*	PCV13 indicated for 6 through 18 Years*	PCV13 indicated for 19 Years or Older	PPSV23 indicated for 2 through 64 Years
Chronic heart or lung disease[†]	Yes	No	No	Yes
Diabetes	Yes	No	No	Yes
Chronic liver disease, including cirrhosis	Yes	No	No	Yes
Cigarette smoking (in adults)	Yes	No	No	Yes
Alcoholism (in adults)	Yes	No	No	Yes
Cerebrospinal Fluid (CSF) leak	Yes	Yes	Yes	Yes
Cochlear implant	Yes	Yes	Yes	Yes
Functional or anatomic asplenia, including sickle cell disease	Yes	Yes	Yes	Yes
Immunocompromising conditions[§]	Yes	Yes	Yes	Yes
Persons living in special environments or social settings[¶]	No	No	No	Consider

*PCV13 only recommended if child is unvaccinated or received incomplete vaccine schedule.

[†]Includes congestive heart failure, cardiomyopathies, chronic obstructive pulmonary disease, emphysema, and asthma. Asthma only included for children (through age 18 years) if treated with high-dose oral corticosteroid therapy.

[§]Includes congenital or acquired immunodeficiencies, Hodgkin's Disease, lymphoma, leukemia, multiple myeloma, generalized malignancy, and other cancers if on immunosuppressive therapy; HIV infection; chronic renal failure; nephrotic syndrome; organ transplant; and immunosuppressive medications, including chemotherapy and high-dose corticosteroid treatment.

[¶]Includes Alaska Native, Navajo, and White Mountain Apache populations.

Children Age 2 Through 23 Months

Children should routinely receive a 3-dose primary series of PCV13 at age 2, 4, and 6 months, and dose 4 (booster) at age 12 through 15 months. Dose 1 can be administered as early as 6 weeks. For doses given before the 1st birthday, the minimum interval between doses is 4 weeks; doses given at age 12 months or older should be separated by at least 8 weeks. PCV13 can be administered at the same time as other routine immunizations.

Unvaccinated children age 7 months or older do not require a full series of four doses. The number of doses depends on the child's current age and the age at which the first dose of PCV13 was administered. If the child's current age is 7 through 11 months, the recommended series is 2 doses at least 4 weeks apart, and a booster dose at age 12 through 15 months. If the vaccination series is initiated at age 7 through 11 months, and the next dose is administered after the 1st birthday, another dose should be administered 8 weeks later. If the child's current age is 12 through 23 months, the recommended series is 2 doses at least 8 weeks apart.

Healthy Children Age 24 through 59 Months

Healthy children age 24 through 59 months should receive 1 dose of PCV13 if child is unvaccinated or received any incomplete schedule. Routine use of PCV13 is not recommended for healthy children age 5 years or older.

Children Age 24 through 71 Months, with Certain Medical Conditions

Children age 24 through 71 months with certain conditions (see table "Conditions with Pneumococcal Vaccination Indications" above) should receive 2 doses of PCV13 separated by 8 weeks if they are unvaccinated or received any incomplete schedule of less than 3 doses. Children with any incomplete schedule of 3 doses should receive 1 dose of PCV13 at least 8 weeks after the most recent dose.

These children should receive a dose of PPSV23 at least 8 weeks after the final dose of PCV13. Additionally, if they are immunocompromised (see table "Conditions with Pneumococcal Vaccination Indications" above for list of conditions) or have functional or anatomic asplenia, they should receive a second dose of PPSV23 five years after the first.

Children and Adolescents Age 6 through 18 Years, with Certain Medical Conditions

Unvaccinated children and adolescents age 6 through 18 years with certain medical conditions (see table "Conditions with Pneumococcal Vaccination Indications" above) should receive both PCV13 and PPSV23. A single dose of PCV13 should be given followed by a dose of PPSV23 at least 8 weeks later. A second dose of PPSV23 is recommended 5 years after the first PPSV23 dose for children with anatomic or functional asplenia, or other immunocompromising conditions (see footnote in table "Conditions with Pneumococcal Vaccination Indications" above for complete list of conditions).

If a complete schedule of PCV13 has been given, no additional PCV13 doses are required. If PCV13 has not been given, and two doses of PPSV23 have already been given, a dose of PCV13 should be given at least 8 weeks after the most recent dose of PPSV23. PCV13 may also be given between two doses of PPSV23.

Some children and adolescents in this age group with certain conditions should only receive one dose of PPSV23, if they have not already.

Pneumococcal Vaccination Schedule for Children and Adolescents Age 6 through 18 years with Certain Chronic or Immunocompromising Conditions

Condition(s)	Prior Pneumococcal Doses	Recommendation
Chronic heart disease, chronic lung disease, diabetes, chronic liver disease (including cirrhosis)	PPSV23 (or PPSV23 & PCV13)	No pneumococcal vaccine needed
	None, or if PCV13 only	• **PPSV23** at least 8 weeks after previous PCV13
Cerebrospinal fluid leak, cochlear implant	None	• **PCV13** • **PPSV23** at least 8 weeks after PCV13
	PCV13 (No PPSV23)	• **PPSV23** at least 8 weeks after previous PCV13
	PPSV23 (No PCV13)	• **PCV13** at least 8 weeks after previous PPSV23
Functional and/or anatomic asplenia (including sickle cell disease), immunocompromising conditions*	None	• **PCV13** • **PPSV23** at least 8 weeks after PCV13 • **PPSV23** at least 5 years after previous PPSV23
	PCV13 (No PPSV23)	• **PPSV23** at least 8 weeks after previous PCV13 • **PPSV23** at least 5 years after 1st PPSV23
	PPSV23 (No PCV13)	• **PCV13** at least 8 weeks after previous PPSV23 • **PPSV23** at least 8 weeks after PCV13 and at least 5 years after previous PPSV23

*Includes congenital or acquired immunodeficiencies, Hodgkin's Disease, lymphoma, leukemia, multiple myeloma, generalized malignancy, and other cancers if on immunosuppressive therapy; HIV Infection; chronic renal failure; nephrotic syndrome; organ transplant; and immunosuppressive medications, including chemotherapy and high-dose corticosteroid treatment.

Adults Age 19 through 64 Years, with Certain Chronic or Immunocompromising Conditions

Routine use of PCV13 or PPSV23 is not recommended for healthy adults age19 through 64 years. Unvaccinated persons age 19 through 64 years with certain chronic conditions (see table "Conditions with Pneumococcal Vaccination Indications" above) should receive one dose of PPSV23 if they have not already.

Unvaccinated persons age 19 years or older with certain immunocompromising conditions, cerebrospinal fluid leak, or cochlear implant (see table "Conditions with Pneumococcal Vaccination Indications", above) should receive a single dose of PCV13 followed by a dose of PPSV23 at least 8 weeks later. If a dose of PPSV23 was given first, PCV13 should be administered at least 1 year later. A second dose of PPSV23 is recommended 5 years after the first PPSV23 dose for adults with anatomic or functional asplenia, or other immunocompromising conditions.

Conditions for Administration of PCV13 and PPSV23 in Adults

Medical Condition(s)	PCV 13 indicated for age 19 years or older	PSV23 indicated for age 19 through 64 years	PPSV23 revaccination indicated for age 19 through 64 years	PCV13 indicated for age 65 years or older	PPSV23 indicated for age 65 years or older
None	No	No	No	Based on shared clinical decision-making	Yes If PCV13 has been given, then give PPSV23 at least 1 year after PCV13
Chronic heart disease, chronic lung disease, diabetes, alcoholism, chronic liver disease (including cirrhosis), current cigarette smoking, asthma	No	Yes	No	Based on shared clinical decision-making	Yes If PCV13 has been given, then give PPSV23 at least 1 year after PCV13 and at least 5 years after any PPSV23 given at less than age 65 years
Cerebrospinal fluid leak, cochlear implant	Yes	Yes At least 8 weeks after PCV 13	No	Yes If no previous PCV13 vaccination	Yes At least 8 weeks after PCV13 and at least 5 years after any PPSV23 given at less than age 65 years
Functional or anatomic asplenia (including sickle cell disease/other hemoglobinopathies)	Yes	Yes At least 8 weeks after PCV13	Yes At least 5 years after first dose of PPSV23	Yes If no previous PCV13 vaccination	Yes At least 8 weeks after PCV13 and at least 5 years after any PPSV23 given at less than age 65 years
Immunocompromising conditions*	Yes	Yes At least 8 weeks after PCV13	Yes At least 5 years after first dose of PPSV23	Yes If no previous PCV13 vaccination	Yes At least 8 weeks after PCV13 and at least 5 years after any PPSV23 given at less than age 65 years

*Includes congenital or acquired immunodeficiencies, Hodgkin's Disease, lymphoma, leukemia, multiple myeloma, generalized malignancy, and other cancers if on immunosuppressive therapy; HIV infection; chronic renal failure; nephrotic syndrome; organ transplant; and immunosuppressive medications, including chemotherapy and high-dose corticosteroid treatment.

Adults Age 65 Years or Older, without Immunocompromising Conditions, Cerebrospinal fluid leak, or Cochlear Implant

A single dose of PPSV23 is recommended for all adults age 65 years or older, regardless of previous pneumococcal vaccination history. If any PPSV23 dose(s) were given before age 65 years, a single, final dose of PPSV23 should be given at age 65 or at least 5 years after the last PPSV23 dose. If PPSV23 was administered at age 65 years or later, no additional doses are needed.

Adults age 65 years or older without immunocompromising conditions (see table "Conditions with Pneumococcal Vaccination Indications" above) may discuss with their clinician and decide whether to receive PCV13 if a dose was not received

before (i.e., shared clinical decision making). If a decision is made to receive PCV13, a dose of PCV13 should be given first, followed by a dose of PPSV23 at least one year later.

Additional Scheduling and Timing Considerations

Additional information on the timing of pneumococcal vaccination for adults and children can be found at https://www.cdc.gov/vaccines/vpd/pneumo/hcp/recommendations.html. PCV13 and PPSV23 should not be administered simultaneously (i.e., on the same clinic day). Studies evaluating immune responses to PCV13 and PPSV23 administered in series showed the immune response was better when PCV13 was given first. The minimum interval between PCV13 and PPSV23 is 8 weeks for adults with immunocompromising conditions and 1 year for immunocompetent adults. However, in adults, if they are administered simultaneously or at an interval less than 8 weeks, neither dose needs to be repeated. In children, if they are administered simultaneously, PCV13 should be repeated at least 8 weeks later.

The target groups for pneumococcal vaccines and influenza vaccines overlap. Either pneumococcal vaccine may be given at the same time as influenza vaccine, if indicated, but at different anatomical sites. Most healthy adults age 65 years or older need only a single lifetime dose of PPSV23 and may be administered PCV13 on or after the 65th birthday based on shared clinical decision making.

While for most other vaccines health care providers should only accept written, dated records as evidence of vaccination, self-reported doses of adult PPSV23 (but not PCV13) are acceptable. Persons with uncertain or unknown vaccination status should be vaccinated.

When elective splenectomy, immunocompromising therapy, or cochlear implant placement is being planned, providers should choose the vaccines appropriate to the level of risk for invasive pneumococcal disease which would exist after the surgery or treatment. For example, a person who will undergo splenectomy should be considered asplenic when applying these vaccine recommendations. The choice of vaccine also depends on past history of pneumococcal vaccination. If PCV13 and PPSV23 are both recommended, they both need to be administered, preferably before treatment or surgery. PCV13 should be administered first, and PPSV23 at least 8 weeks later. PPSV23 should be given at least 2 weeks before the treatment or surgery. If treatment or surgery cannot be delayed, providers can consider administering pneumococcal vaccines afterward.

Following vaccination with PPSV23, antibody levels decline after 5 to 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 for adults, so the ability to define the need for revaccination based only on serology is limited. In addition, currently available pneumococcal polysaccharide vaccine elicits a T-cell-independent response, and does not produce a sustained increase ("boost") in antibody titers. Available data do not indicate a substantial increase in antibody level in the majority of revaccinated persons.

Pneumococcal Vaccine Efficacy

- PPSV23
  - 60-70% effective in preventing invasive disease caused by serotypes in vaccine
- PCV13
  - Induces levels of antibodies comparable to those induced by PCV7, which was shown to reduce invasive disease caused by vaccine serotypes by 97% in children
  - 45.6% efficacy against vaccine-type pneumococcal pneumonia, 45.0% efficacy against vaccine-type nonbacteremic pneumococcal pneumonia, 75.0% efficacy against vaccine-type IPD in adults

Immunogenicity and Vaccine Efficacy

Pneumococcal Polysaccharide Vaccine

More than 80% of healthy adults who receive PPSV23 develop antibodies against the serotypes contained in the vaccine, usually within 2 to 3 weeks after vaccination. Older adults and persons with some chronic illnesses or immunodeficiency may not respond as well, if at all. Elevated antibody levels following vaccination persist for at least 5 years in healthy adults but decline more quickly in persons with certain underlying illnesses. In children younger than age 2 years, antibody response to PPSV23 is generally poor.

PPSV23 vaccine efficacy studies have resulted in various estimates of clinical effectiveness. Overall, the vaccine is 60% to 70% effective in preventing invasive disease caused by serotypes included in the vaccine. Despite the vaccine's reduced effectiveness among immunocompromised persons,

PPSV23 is still recommended for such persons because they are at increased risk of developing severe disease. There is no consensus regarding the ability of PPSV23 to prevent non-bacteremic pneumococcal pneumonia. For this reason, providers should avoid referring to PPSV23 as a "pneumonia vaccine."

Studies comparing patterns of pneumococcal carriage before and after PPSV23 vaccination have not shown clinically significant decreases in carriage rates among vaccine recipients.

Pneumococcal Conjugate Vaccine

In a large clinical trial, PCV7 was shown to reduce invasive disease caused by vaccine serotypes by 97%. Children who received PCV7 had 20% fewer episodes of chest X-ray confirmed pneumonia, 7% fewer episodes of acute otitis media, and underwent 20% fewer tympanostomy tube placements than did unvaccinated children. There is evidence that PCV7 reduced nasopharyngeal carriage among children of pneumococcal serotypes included in the vaccine.

PCV13 was licensed in the United States based upon studies that compared the serologic response of children who received PCV13 to those who received PCV7. These studies showed that PCV13 induced levels of antibodies that were comparable to those induced by PCV7 and shown to be protective against invasive disease.

In another study of PCV13, children age 7 through 11 months, 12 through 23 months, and 24 through 71 months who had not received pneumococcal conjugate vaccine doses previously were administered 1, 2, or 3 doses of PCV13 according to age-appropriate immunization schedules. These schedules resulted in antibody responses to each of the 13 serotypes that were comparable to those achieved after the 3-dose infant PCV13 series in the U.S. immunogenicity trial, except for serotype 1, for which IgG geometric mean concentration (GMC) was lower among children age 24 through 71 months.

Licensure of PCV13 for adults age 50 years or older was based on serologic studies comparing immune response of PCV13 recipients to immune response following a dose of PPSV23. In two randomized, multicenter immunogenicity studies conducted in the United States and Europe, immunocompetent adults age 50 years or older received a single dose of PCV13 or PPSV23. In adults age 60 through 64 years and age 70 years or older, PCV13 elicited opsonophagocytic activity geometric mean antibody titers that were comparable with, or higher than, responses elicited by PPSV23. Persons who received PPSV23 as the initial study dose had lower opsonophagocytic antibody

responses after subsequent administration of a PCV13 dose 1 year later than those who had received PCV13 as the initial dose. Since introduction of PCV13 in children in 2010, invasive disease caused by PCV13 serotypes has declined over 60% among adults age 65 years or older through PCV13 indirect effects.

A randomized placebo-controlled trial was conducted in the Netherlands among approximately 85,000 adults age 65 years or older during 2008–2013 to evaluate the clinical benefit of PCV13 in the prevention of pneumococcal pneumonia. The results of this trial demonstrated 45.6% efficacy of PCV13 against vaccine-type pneumococcal pneumonia, 45.0% efficacy against vaccine-type nonbacteremic pneumococcal pneumonia, and 75.0% efficacy of PCV13 against vaccine-type IPD.

Pneumococcal Vaccine Contraindications and Precautions

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

Contraindications and Precautions to Vaccination

As with other vaccines, a history of a severe allergic reaction (anaphylaxis) to a vaccine component or following a prior dose is a contraindication to further doses. Moderate or severe acute illness (with or without fever) in a patient is considered a precaution to vaccination, although persons with minor illness may be vaccinated.

Pneumococcal Vaccine Safety

- PPSV23
  - Pain, soreness, tenderness, injection site swelling, induration, headache, fatigue, muscle pain
- PSV13
  - Pain, tenderness, swelling, erythema, decreased appetite, fatigue, headache, muscle pain, irritability, fever
  - Simultaneous administration of PCV13 and inactivated influenza vaccine associated with an increased risk of febrile seizures

Vaccine Safety

Studies support the safety of PCV13 and PPSV23 in children and adults.

Pneumococcal Polysaccharide Vaccine

In pre-licensure PPSV23 studies, the most common adverse reactions reported were local reactions (pain, soreness, tenderness, injection-site swelling, and induration), headache, fatigue, and muscle pain. These reactions usually resolved within 48 hours. In study participants age 65 years or older, systemic adverse reactions that were related to the vaccine were more frequent following the second dose than the first dose.

Results from studies done after PPSV23 was licensed have been consistent with the safety findings in the pre-licensure studies. A transient increase in viral replication among HIV-positive persons has been reported following PPSV23 vaccine. No clinical or immunologic deterioration has been reported in these persons.

Pneumococcal Conjugate Vaccine

In the pre-licensure studies, the common adverse reactions reported were local reactions (pain, tenderness, swelling and erythema), decreased appetite, fatigue, headache, muscle pain, irritability, and fever. Increased and decreased sleep was also commonly reported in infants and toddlers.

In young children, studies done after PCV13 was licensed showed simultaneous PCV13 and inactivated influenza vaccine was associated with an increased risk of febrile seizures during some influenza seasons. Febrile seizures can be concerning to caregivers, but they are brief and are not associated with any long-term complications. A review of adverse events reported to the Vaccine Adverse Event Reporting System after PCV13 vaccination in children age 6 weeks through 59 months was consistent with the pre-licensure studies.

Vaccination in Pregnancy

ACIP recommendations for use of PCV13 during pregnancy do not exist.

The safety of PPSV23 vaccine for pregnant women has not been studied, although no adverse consequences have been reported among newborns whose mothers were inadvertently vaccinated during pregnancy. Women who are at increased risk of pneumococcal disease and who are candidates for pneumococcal vaccine should be vaccinated before pregnancy, if possible.

Vaccine Storage and Handling

PCV13 and PPSV23 should be maintained at refrigerator temperature between 2°C and 8°C (36°F and 46°F). Manufacturer package inserts contain additional information. For complete information on best practices and recommendations for vaccine storage and handling, please refer to CDC's Vaccine Storage and Handling Toolkit, www.cdc.gov/vaccines/hcp/admin/storage/toolkit/storage-handling-toolkit.pdf.

Surveillance and Reporting of Pneumococcal Disease

Invasive pneumococcal disease is a notifiable condition in most states. For information on guidance for state and local health department staff who are involved in surveillance activities for vaccine-preventable diseases, please consult the Manual for the Surveillance of Vaccine-Preventable Diseases, www.cdc.gov/vaccines/pubs/surv-manual/chapters.html.

NOTES

Acknowledgements

The editors would like to acknowledge Tamara Pilishvili and Ginger Redmon for their contributions to this chapter.

Selected References

Arana J, Moro P, Lewis P, et al. Post-licensure surveillance of 13-valent pneumococcal conjugate vaccine (PCV13) in children 6 weeks–59 months old, Vaccine Adverse Event Reporting System (VAERS), United States, 2010-2017. *Open Forum Infect Dis* 2017;4(Suppl 1):S464.

Black S, Shinefield H, Fireman B, et al. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Northern California Kaiser Permanente Vaccine Study Center Group. *Pediatr Infect Dis J* 2000;19(3):187–95.

CDC. Active Bacterial Core surveillance. http://www.cdc.gov/abcs/. Accessed October 22, 2020.

CDC. Antibiotic resistance threats in the United States, 2019. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2019. Available at: https://www.cdc.gov/drugresistance/Biggest-Threats.html.

CDC. Intervals between PCV13 and PPSV23 vaccines. *MMWR* 2015;64(34):944–7.

CDC. Invasive pneumococcal disease in young children before licensure of 13-valent pneumococcal conjugate vaccine — United States, 2007. *MMWR* 2010;59(9):253–7.

CDC. Pneumococcal vaccines. https://www.cdc.gov/vaccinesafety/vaccines/pneumococcal-vaccine.html. Accessed October 22, 2020.

CDC. Prevention of pneumococcal disease among infants and children - use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2010;59(RR-11):1–18.

CDC. Updated recommendations for prevention of invasive pneumococcal disease among adults using the 23-valent pneumococcal polysaccharide vaccine (PPSV23). *MMWR* 2010; 59(34);1102–1106.

CDC. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged ≥65 years: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2014;63(37):822–825.

CDC. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged ≥65 years: updated recommendations of the Advisory Committee on Immunization Practices. *MMWR* 2019;68(46):1069–75.

CDC. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2012;61(40):816-9.

CDC. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among children aged 6-18 years with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2013;62(25):521–4.

Food and Drug Administration. Prescribing information (package insert). Pneumovax 23 (pneumococcal vaccine, polyvalent). Silver Spring, MD: U.S. Department of Health and Human Services, Food and Drug Administration; 2020. https://www.fda.gov/vaccines-blood-biologics/vaccines/pneumovax-23-pneumococcal-vaccine-polyvalent. Accessed October 22, 2020.

Food and Drug Administration. Prescribing information (package insert). Prevnar 13 (pneumococcal 13-valent conjugate vaccine). Silver Spring, MD: U.S. Department of Health and Human Services, Food and Drug Administration; 2017. https://www.fda.gov/vaccines-blood-biologics/vaccines/prevnar-13. Accessed October 22, 2020.

Jackson L, Benson P, Sneller V, et al. Safety of revaccination with pneumococcal polysaccharide vaccine. *JAMA* 1999;281(3):243–8.

Li R, Stewart B, McNeil M, et al. Post licensure surveillance of influenza vaccines in the Vaccine Safety Datalink in the 2013-2014 and 2014-2015 seasons. *Pharmacoepidemiol Drug Safe* 2016;25(8):928–34.

Miller E, Moro P, Cano M, et al. Post-licensure safety surveillance of 23-valent pneumococcal polysaccharide vaccine in the Vaccine Adverse Event Reporting System (VAERS), 1990-2013. *Vaccine* 2016;34(25):2841–6.

Pichichero M, Kaur R, Scott D, et al. Effectiveness of 13-valent pneumococcal conjugate vaccination for protection against acute otitis media caused by Streptococcus pneumoniae in healthy young children: a prospective observational study. *Lancet Child Adolesc Health*. 2018;2(8):561–8

NOTES

NOTES

Pilishvili T, Lexau C, Farley M, et al. Sustained reductions in invasive pneumococcal disease in the era of conjugate vaccine. *J Infect Dis* 2010;201(1):32–41.

Said M, Johnson H, Nonyane B, et al. Estimating the burden of pneumococcal pneumonia among adults: a systematic review and meta-analysis of diagnostic techniques. *PLoS One* 2013;8(4):e60273.

Thigpen M, Whitney C, Messonnier N, et al. Bacterial meningitis in the United States, 1998-2007. *N Engl J Med* 2011;364(21):2016–25.

Tse A, Tseng H, Greene S, et al. Signal identification and evaluation for risk of febrile seizures in children following trivalent inactivated influenza vaccine in the Vaccine Safety Datalink Project, 2010-2011. *Vaccine* 2012;30(11):2024–31.

Tseng H, Sy L, Qian L, et al. Pneumococcal conjugate vaccine safety in elderly adults. *Open Forum Infect Dis* 2018;5(6):ofy100.

Williams W, Lu P, O'Halloran A, et. al. Surveillance of Vaccination Coverage Among Adult Populations - United States, 2014. *MMWR Surveill Summ* 2016;65(1):1–36.

Concepcion F. Estivariz, MD; Ruth Link-Gelles, PhD, MPH; and Tom Shimabukuro, MD, MPH, MBA

Descriptions of polio-like illnesses have been around since antiquity, including a funerary stele depicting a man with a withered leg leaning on a staff. Michael Underwood first described a debility of the lower extremities in children that was recognizable as poliomyelitis in England in 1789, but the disease was not observed in epidemics until the late 19th century. During the first half of the 20th century, developed countries in the Northern Hemisphere suffered epidemics each summer and fall that became increasingly severe. Polio infections peaked in the United States in 1952, with more than 21,000 paralytic cases. Following introduction of effective vaccines in 1955 (inactivated polio vaccine, IPV) and 1961 (oral poliovirus vaccine, OPV), polio incidence declined rapidly. The last case of wild poliovirus acquired in the United States was in 1979.

Poliomyelitis

- First described by Michael Underwood in 1789
- Developed countries in Northern Hemisphere suffered increasingly severe epidemics in the first half of the 20th century
- More than 21,000 paralytic cases reported in the U.S. in 1952
- Last case of wild poliovirus acquired in the U.S. was 1979

Poliovirus

Poliovirus is a member of the enterovirus subgroup, family Picornaviridae. Picornaviruses are small, ether-insensitive viruses with an RNA genome.

There are three poliovirus serotypes (type1, type 2, and type 3); immunity to one serotype does not produce significant immunity to the other serotypes.

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

Poliovirus

- Enterovirus (RNA)
- Three serotypes: type 1, type 2, type 3
- Immunity to one serotype does not produce significant immunity to other serotypes
- Rapidly inactivated by heat, formaldehyde, chlorine, ultraviolet light

Pathogenesis

The virus enters through the mouth and multiplies in the oropharynx and gastrointestinal tract. The virus is usually present in nasopharyngeal secretions for 1 to 2 weeks and can be shed in stools for several weeks after infection, even in individuals with minor symptoms or no illness. During intestinal replication, the virus invades local lymphoid tissue and may enter the bloodstream, and then infect cells of the central nervous system. Poliovirus-induced destruction of motor neurons of the anterior horn of the spinal cord and brain stem cells results in distinctive paralysis.

Poliomyelitis Pathogenesis

- Entry through mouth
- Replication in oropharynx, gastrointestinal tract
- Invades local lymphoid tissue and may enter the bloodstream, and then infect cells of the central nervous system
- Destruction of motor neurons result in distinctive paralysis

Clinical Features

The incubation period for nonparalytic poliomyelitis is 3 to 6 days. For the onset of paralysis in paralytic poliomyelitis, the incubation period is usually 7 to 21 days. The risk of severe disease and death following primary infection with poliovirus increases with increasing age.

Approximately 70% of all polio infections in children are asymptomatic. Infected individuals without symptoms shed the

Poliomyelitis Clinical Features

- Incubation period
  - 3 to 6 days for nonparalytic poliomyelitis
  - 7 to 21 days for onset of paralysis in paralytic poliomyelitis
- Paralysis is often permanent
- Paralytic disease may be caused by wild-type polioviruses, attenuated polioviruses in oral vaccine, or by vaccine-derived polioviruses

virus in nasopharyngeal secretions and stool for several days or weeks and are able to transmit the virus to others.

Approximately 24% of polio infections in children 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 a low fever, sore throat, and complete recovery in less than a week.

Nonparalytic aseptic meningitis occurs in 1% to 5% of polio infections in children. The clinical presentation includes stiffness of the neck, back, or legs, usually following several days of a prodrome similar to that of minor illness. Increased or abnormal sensations (e.g., pain in the limbs, back, or neck), headache, and vomiting can also occur. Typically, symptoms last 2 to 10 days and are followed by complete recovery.

Less than 1% of all polio infections in children result in flaccid paralysis. The course may be biphasic in children, with initial minor illness that lasts several days, a symptom-free period of 1 to 3 days, followed by the major illness with paralysis, fever and muscle pain. Paralysis usually progresses within 2 to 3 days. Among adolescents and adults, the minor illness is often absent and they suffer more severe pain and paralysis. Paralysis is typically asymmetrical, more severe proximally, and associated with absent or reduced deep tendon reflexes and intact sensation. Patients usually do not experience changes in cognition.

Paralysis is often permanent, although total or partial recovery can occur through compensation by muscles not affected. Weakness or paralysis present 12 months after onset, which occurs in two-thirds of patients with paralysis, is usually permanent.

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

The case fatality ratio for paralytic polio is generally 2% to 5% among children and up to 15% to 30% among adolescents and adults. It increases to 25% to 75% with bulbar involvement.

Paralytic disease with similar clinical manifestations may be caused by naturally occurring wild-type polioviruses, by the attenuated polioviruses contained in the oral poliovirus vaccine (Sabin strains) in extremely rare occasions, or by vaccine-derived

polioviruses (VDPVs), which are Sabin vaccine strains that have reverted and re-acquired the virulence and transmissibility of wild polioviruses.

After an interval of 15 to 40 years, 25% to 40% of persons who contracted paralytic poliomyelitis in childhood experience new muscle pain and exacerbation of existing weakness or develop new weakness or paralysis. This disease entity is referred to as post-polio syndrome. Post-polio syndrome is not an infectious process, and persons experiencing this syndrome do not shed poliovirus.

Laboratory Testing

The greatest yield for poliovirus is from viral culture of stool specimen; it is less likely to be recovered from the pharynx, and only rarely recovered from cerebrospinal fluid (CSF) or blood. If poliovirus is isolated, reverse transcriptase polymerase chain reaction (RT-PCR) and genomic sequencing are used to determine the serotype (i.e., 1, 2, or 3), and whether the virus is a wild, vaccine (Sabin), or VDPV strain.

Because viral shedding may be intermittent and the amount of virus declines after paralysis onset, it is recommended to collect two stool specimens at least 24 hours apart and within 14 days of onset of symptoms. Poliovirus may be detected during the first 3 to 10 days after paralysis onset in oropharyngeal specimens, but stool specimens are preferred.

Serology

Serology for all three types of poliovirus is currently not available in most laboratories because of new regulations for poliovirus containment. Furthermore, serology has several limitations. Two specimens are needed, one early in the course of the illness and another three weeks later. A four-fold rise in the titer of the second specimen suggests poliovirus infection, and two negative specimens may rule out poliovirus infection. However, immunocompromised patients may have two titers with no antibody detected and still be infected with poliovirus. Among immunocompetent patients, the four-fold increase may not be observed because neutralizing antibodies appear early and may exist at the time of hospitalization, or the patient may have antibodies from prior vaccination.

Poliovirus Epidemiology

- Reservoir
  - Human
- Transmission
  - Fecal-oral or oral-oral
- Temporal pattern
  - Peaks in the summer in temperate climates; no season pattern in tropical climates
- Communicability
  - Highly infectious days before and after onset of symptoms
  - Most infectious in the days immediately before and after onset of symptoms

Epidemiology

Occurrence

At one time, poliovirus infection occurred throughout the world. Vaccination resulted in reduced circulation of wild poliovirus and its elimination from the United States in 1979. A polio eradication program conducted by the Pan American Health Organization led to elimination of polio in the Western Hemisphere in 1991. The Global Polio Eradication Program has

dramatically reduced wild poliovirus transmission throughout the world. Type 2 and 3 wild poliovirus have been eradicated worldwide and endemic circulation of type 1 wild poliovirus persists only in two countries.

Reservoir

Humans are the only known reservoir of poliovirus, which is transmitted most frequently by persons with inapparent infections. There is no asymptomatic carrier state except in immunocompromised persons.

Transmission

Person-to-person spread of poliovirus occurs via the fecal-oral or oral-oral routes. The fecal-oral route is the most important transmission pathway in settings with suboptimal hygiene and sanitation.

Temporal Pattern

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

Communicability

Poliovirus is highly infectious, with seroconversion rates among susceptible household contacts of children nearly 100%, and greater than 90% among susceptible household contacts of adults. Persons infected with poliovirus are most infectious in the days immediately before and after the onset of symptoms, but poliovirus may remain present in the stool for up to 6 weeks.

Poliovirus Secular Trends in the United Status

- Before the 18th century, polioviruses probably circulated widely
- In immediate prevaccine era, improved sanitation resulted in less frequent exposure and increased age of primary infection, resulting in large epidemics with high death count
- Incidence dramatically decreased following inactivated polio vaccine (IPV) introduction in 1955
- Last cases of locally-acquired paralytic poliomyelitis caused by wild poliovirus in the U.S. reported in 1979
- Last case of vaccine-associated paralytic polio (VAPP) acquired in the U.S. reported in 1999

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 and protected infants from infection-causing paralysis.

In the immediate prevaccine era, during the first half of the 20th century, improved sanitation resulted in less frequent exposure and increased the age of primary infection, resulting in large epidemics with high numbers of deaths. The incidence dramatically decreased after the introduction of inactivated polio vaccine (IPV) in 1955 and continued to decline following oral polio vaccine (OPV) introduction in 1961. From the more than 21,000 paralytic cases reported in 1952, only 2,525 cases were reported in 1960 and 61 cases in 1965.

The last cases of locally-acquired paralytic poliomyelitis caused by wild poliovirus in the United States were reported in 1979, during an outbreak in Amish communities in several

Midwestern states. Epidemiologic and virologic evidence indicated that this outbreak was seeded by an importation from the Netherlands.

From 1980–1999, 162 confirmed cases of paralytic poliomyelitis were reported in the United States, an average of 8 cases per year. Six cases were caused by wild poliovirus acquired outside the United States and two cases were classified as indeterminant (no poliovirus isolated from samples obtained from the patients, and patients had no history of recent vaccination or direct contact with a vaccine recipient). The remaining 154 (95%) cases were vaccine-associated paralytic polio (VAPP) caused by the Sabin poliovirus strains contained in OPV vaccine.

In order to eliminate VAPP from the United States, the Advisory Committee on Immunization Practices (ACIP) recommended in 2000 exclusive use of IPV vaccine. The last case of VAPP acquired in the United States was reported in 1999. Paralysis caused by VDPV was reported in an immunocompromised person in 2009, who was likely infected with vaccine poliovirus 12 years prior to the onset of paralysis. In 2005, asymptomatic infections with a circulating VDPV were detected in several unvaccinated children in Minnesota. The source of the virus was not determined, but it appeared to have been circulating undetected in an unidentified location, possibly another country, for at least 2 years based on genetic changes in the virus.

Among children born during 2015 or 2016, 92.7% had received at least 3 doses of poliovirus vaccine by age 24 months, compared to 91.7% for children born during 2013 or 2014.

Eradication

Following the widespread use of poliovirus vaccine in the mid-1950s, the incidence of poliomyelitis declined rapidly in many industrialized countries.

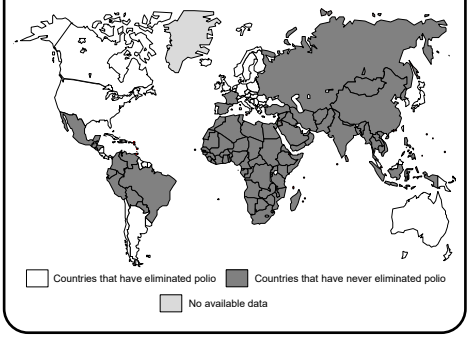
In 1985, the member countries of the Pan American Health Organization adopted the goal of eliminating poliomyelitis from the Western Hemisphere by 1990. The strategy to achieve this goal included increasing vaccination coverage; enhancing surveillance for suspected cases (i.e., surveillance for acute flaccid paralysis); and using supplemental immunization strategies such as national immunization days, house-to-house vaccination, and containment activities. In 1994, an international commission certified the Western Hemisphere to be free of indigenous wild poliovirus.

Following the success in the Americas, the World Health Assembly adopted the goal of global eradication of poliovirus in 1988. The polio eradication initiative is led by a coalition of

Poliomyelitis Eradication

- **Mid-1950s**—Widespread use of poliovirus vaccine
- **1988**—Polio paralyzed ~350,000 individuals per year in more than 125 countries
- **1994**—Western Hemisphere free of indigenous wild poliovirus
- **2015**—Type 2 wild poliovirus eradicated
- **2019**—Type 3 wild poliovirus eradicated
- **2019**—Only 125 cases caused by wild poliovirus globally (99% reduction from 1988) and endemic in only two countries
- **2019**—Low routine immunization and poor vaccination campaigns resulted in re-emergence of type 2 VDPV

Wild Poliovirus 1988



Wild Poliovirus 2018

international organizations including WHO, the United Nations Children's Fund (UNICEF), CDC, Rotary International, the Bill and Melinda Gates Foundation, and Gavi.

Substantial progress has been made towards polio eradication. In 1988, polio paralyzed an estimated 350,000 individuals per year in more than 125 countries. By 2019, only 125 cases caused by wild poliovirus were reported globally, a reduction of more than 99% from 1988, and polio remained endemic in only two countries. The Global Commission for the Certification of Poliomyelitis Eradication declared type 2 wild poliovirus eradicated in 2015 and type 3 wild poliovirus eradicated in 2019. Unfortunately, low coverage with routine immunization and poor quality of vaccination campaigns conducted before the trivalent-to-bivalent switch have resulted in re-emergence of type 2 VDPV. In 2019, circulating type 2 VDPV caused outbreaks in 20 countries in Africa and Asia and paralyzed 369 children.

Poliovirus Vaccines

- IPV (IPOL)
- Combination vaccines
  - DTaP-HepB-IPV (Pediarix)
  - DTaP-IPV/Hib (Pentacel)
  - DTaP-IPV (Kinrix)
  - DTaP-IPV (Quadracel)
  - DTaP-IPV-Hib-HepB (Vaxelis) (licensed but not yet available for use)

Poliovirus Vaccines

Inactivated poliovirus (IPV) vaccine was licensed for use in 1955 and was used extensively from that time until the early 1960s.

In 1961, type 1 and 2 monovalent oral poliovirus (mOPV) vaccines were licensed, followed by type 3 mOPV vaccine in 1962, and trivalent OPV (tOPV) vaccine in 1963. Oral poliovirus (OPV) vaccine contains live poliovirus strains (Sabin) derived from wild polioviruses and attenuated by repeated passages through cells to induce mutations that reduce their neurovirulence and transmissibility.

Upon ingestion of OPV vaccine, the live attenuated polioviruses replicate in the intestinal mucosa and lymphoid cells in the oropharynx and intestine, in a similar manner to wild poliovirus infection. Vaccine viruses are excreted in the stool of the vaccinated person for up to 6 weeks after a dose, with maximum shedding in the first 1 to 2 weeks after vaccination. Vaccine viruses may spread from the recipient to contacts. Persons in contact with fecal material of a vaccinated person may be exposed and infected with vaccine virus. Replication and shedding of vaccine virus in stools may occur upon intake of a new OPV vaccine dose, but the duration of shedding is usually short and virus concentration in stools is lower.

Trivalent OPV vaccine largely replaced IPV vaccine as the vaccine of choice in the United States and most other countries of the world until the late 1990s. The nearly exclusive use of tOPV vaccine led to elimination of wild poliovirus from the United States in less than 20 years. However, one case of VAPP occurred for every 2 to 3 million doses of tOPV vaccine administered. The burden of VAPP in industrialized countries resulted in progressive discontinuation of OPV vaccine.

In 1996, the Advisory Committee on Immunization Practices (ACIP) recommended an increase in use of IPV through a sequential schedule of IPV followed by tOPV to reduce the occurrence of VAPP. The sequential schedule eliminated VAPP among vaccine recipients by producing humoral immunity to polio with inactivated polio vaccine prior to exposure to live vaccine virus. Since tOPV was still used for the third and fourth doses, a risk of VAPP would continue to exist among contacts of vaccine recipients, 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 1998–1999, suggesting an impact of the increased use of IPV vaccine. To further the goal of complete elimination of paralytic polio in the United States, in 1999 ACIP recommended that IPV vaccine be used exclusively. Exclusive use of IPV vaccine eliminated the shedding of live vaccine virus, eliminating any indigenous VAPP.

Among the 3 wild poliovirus types, type 2 was declared eradicated in 2015. To remove the risk for infection with circulating type 2 VDPV (cVDPV2), in 2016 all OPV-using countries simultaneously switched from tOPV to bivalent OPV (bOPV) vaccine, which contains only types 1 and 3 polioviruses, following a directive from the World Health Organization. One or several doses of IPV vaccine is used in all countries, either exclusively or in combined schedules with bOPV. Use of mOPV2 in response to cVDPV2 outbreaks must be approved by the Director General of the WHO; the mOPV2 Advisory Group makes recommendations for use.

Two single-antigen inactivated poliovirus (IPV) products are currently licensed for use in the United States, but only one vaccine, IPOL, is currently distributed.

There are five combination vaccines that contain IPV vaccine. DTaP-HepB-IPV (Pediarix), DTaP-IPV/Hib (Pentacel), DTaP-IPV (Kinrix), DTaP-IPV (Quadracel), and DTaP-IPV-Hib-HepB (Vaxelis) are licensed and available for use in the United States.

Characteristics

IPV contains wild poliovirus strains grown individually in Vero cells and inactivated with formaldehyde. The initial formula developed by Jonas Salk in the 1950s was replaced by an enhanced potency formula in the late 1980s, which contains 40:8:32 units of serotypes 1, 2, and 3, respectively. IPV vaccine is administered by either subcutaneous or intramuscular injection. Each dose of IPV vaccine contains antibiotics neomycin, streptomycin, and polymyxin B, and the preservative 2-phenoxyethanol. It contains no adjuvant. Specific ingredients to combination vaccines containing IPV vaccine differ.

Poliovirus Vaccine Characteristics (IPV)

- Grown in monkey kidney (Vero) cells
- Inactivated with formaldehyde
- Contains serotypes 1, 2, and 3
- Administered by either subcutaneous or intramuscular injection
- Contains neomycin, streptomycin, polymyxin B, 2-phenoxyethanol

Polio Vaccination Schedule (IPV)

- Typically administered at age 2, 4, 6 through 18 months, and 4 through 6 years
- Recommended interval between each of the first 3 doses is 2 months
- Recommended interval between dose 3 and dose 4 is at least 6 months
- Minimum interval between doses is 4 weeks*
- Minimum age for dose 1 is 6 weeks*
- A dose on or after age 4 years is recommended regardless of number of previous doses

*Recommended only if vaccine recipient is at risk for imminent exposure to circulating poliovirus (e.g. outbreak or travel to endemic region)

Vaccination Schedule and Use

The first dose of IPV vaccine may be administered as early as age 6 weeks but is usually administered at age 2 months, with a second dose at age 4 months. The third dose should be given at age 6 through 18 months of age. The recommended interval between the doses in the primary series is 2 months. However, if accelerated protection is needed, the minimum interval between each of the first 3 doses of IPV vaccine is 4 weeks. The final dose in the IPV series should be administered at age 4 through 6 years and at least 6 months after the previous dose. A dose of IPV vaccine on or after age 4 years is recommended regardless of the number of previous doses.

Shorter intervals between doses or beginning the series at a younger age may lead to lower seroconversion rates. Consequently, the use of the minimum age (6 weeks) and minimum intervals between doses in the first 6 months of life is recommended only if the vaccine recipient is at risk for imminent exposure to circulating poliovirus (e.g., during an outbreak or because of travel to a polio-endemic region).

IPV vaccine should be given at the same visit as other recommended vaccines.

Combination Vaccines

DTaP-HepB-IPV (Pediarix)

DTaP-HepB-IPV vaccine is approved for use as a 3-dose series for children age 6 weeks through 6 years. It is administered to infants at age 2, 4, and 6 months. The minimum intervals for DTaP-HepB-IPV vaccine are determined by the DTaP component. The 3 doses must be separated by at least 4 weeks between doses. Because the minimum age for the first dose of DTaP-HepB-IPV vaccine is 6 weeks, this vaccine cannot be used for the birth dose of hepatitis B (HepB) vaccine. The final dose of DTaP-HepB-IPV vaccine should be administered at age 24 weeks or older, the minimum age for completion of the hepatitis B vaccine series. When DTaP-HepB-IPV vaccine is used to provide 3 doses at age 2, 4, and 6 months (based on the DTaP and IPV schedules), this will result in a 4-dose HepB vaccine series, which is acceptable.

DTaP-IPV/Hib (Pentacel)

DTaP-IPV/Hib vaccine is approved for use as a 4-dose series for children age 6 weeks through 4 years. It is administered to infants at age 2, 4, 6, and 15 through 18 months. The minimum intervals for DTaP-IPV/Hib vaccine are determined by the DTaP component. The first 3 doses must be separated by at least 4 weeks between doses. Dose 4 must be separated from dose 3 by at least 6 months, and should not be administered before age 12 months. When DTaP-IPV/Hib vaccine is used to provide 4 doses at age 2, 4, 6, and between 15 through 18 months (based on the DTaP and Hib schedules), an additional

booster dose with IPV-stand alone or DTaP-IPV vaccine should be administered at age 4 through 6 years. This will result in a 5-dose IPV vaccine series, which is acceptable.

DTaP-IPV-Hib-HepB (Vaxelis)

DTaP-IPV-Hib-HepB is approved for use as a 3-dose series for children age 6 weeks through 4 years. It is administered to infants at age 2, 4, and 6 months. The minimum intervals for DTaP-IPV-Hib-HepB vaccine are determined by the DTaP component. The 3 doses must be separated by at least 4 weeks between doses. Because the minimum age for the first dose of DTaP-IPV-Hib-HepB vaccine is 6 weeks, this vaccine cannot be used for the birth dose of hepatitis B (HepB) vaccine. The final dose of DTaP-IPV-Hib-HepB vaccine should be administered at age 24 weeks or older, the minimum age for completion of the hepatitis B vaccine series. When DTaP-IPV-Hib-HepB vaccine is used to provide 3 doses at age 2, 4, and 6 months (based on the DTaP and IPV schedules), this will result in a 4-dose HepB vaccine series, which is acceptable.

DTaP-IPV (Kinrix)

DTaP-IPV (Kinrix) vaccine is approved only for dose 5 of DTaP vaccine and dose 4 of IPV vaccine in children age 4 through 6 years whose previous DTaP vaccine doses have been with Infanrix and/or Pediarix for dose 1, 2, and 3 and Infanrix for dose 4. However, if DTaP-IPV (Kinrix) vaccine is administered to children who received another brand of DTaP vaccine for prior DTaP vaccine doses, or if administered as dose 1, 2, 3, or 4 of the DTaP vaccine series or dose 1, 2, or 3 of the IPV vaccine series, the dose of DTaP-IPV (Kinrix) does not need to be repeated.

DTaP-IPV (Quadracel)

DTaP-IPV (Quadracel) vaccine is approved only for dose 5 of DTaP vaccine and dose 4 or 5 of IPV vaccine in children age 4 through 6 years who have received 4 doses of Pentacel and/or Daptacel vaccine. However, if DTaP-IPV (Quadracel) vaccine is administered to children who received another brand of DTaP vaccine for prior DTaP vaccines doses, or if administered as dose 1, 2, 3, or 4 of the DTaP vaccine series or dose 1, 2, or 3 of the IPV series, the dose of DTaP-IPV (Quadracel) does not need to be repeated.

Polio Vaccination of Adults

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

Some adults, however, are at increased risk of exposure to poliovirus. These include laboratory workers handling specimens that may contain polioviruses, healthcare personnel

Poliovirus Vaccination of Adults

- Routine vaccination of adults age 18 or older in the U.S. is not necessary or recommended
- Laboratory workers handling poliovirus-containing specimens, healthcare personnel treating patients with possible polio, and travelers to areas where poliomyelitis is endemic or epidemic may need vaccination
  - Adults at risk without record of polio vaccination should receive primary immunization

treating patients who could have polio or have close contact with a person who could be infected with poliovirus, and travelers to areas where poliomyelitis is endemic or epidemic.

Recommendations for poliovirus vaccination of these adults depends upon previous vaccination history and time available before protection is required.

When an adult at increased risk of exposure to poliomyelitis has never received polio vaccine or does not have a written record of polio vaccination, primary immunization with IPV is recommended. The recommended schedule is 2 doses separated by 1 to 2 months, and a third dose administered 6 to 12 months after the second dose. The minimum interval between dose 2 and dose 3 is 6 months.

In some circumstances time will not allow completion of this schedule. If 8 weeks or more are available before protection is needed, 3 doses of IPV vaccine should be given at least 4 weeks apart. If 4 to 8 weeks are available before protection is needed, 2 doses of IPV vaccine should be given at least 4 weeks apart. If less than 4 weeks are available before protection is needed, a single dose of IPV vaccine 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.

Poliovirus Vaccine Efficacy (IPV)

- Highly effective in producing immunity to poliovirus
- 90% or more immune after 2 doses
- At least 99% immune after 3 doses
- Duration of immunity not known with certainty, although probably lifelong

Immunogenicity and Vaccine Efficacy

IPV vaccine 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.

IPV vaccine prevents wild poliovirus from reaching the central nervous system in recipients, thus preventing paralysis. Protection against paralytic disease correlates with the presence of antibody after vaccination. IPV vaccine appears to produce less local gastrointestinal immunity than does OPV vaccine. Individuals who receive IPV vaccine usually do not shed virus in nasopharynx but excrete virus in stools following exposure to wild or vaccine poliovirus. The duration of shedding and amount of virus in the stool of IPV-vaccinated individuals is similar to that of unvaccinated individuals, if they have never been exposed to live poliovirus (vaccine or wild). The duration of immunity with IPV is not known with certainty, although it probably provides lifelong immunity after a complete series.

OPV vaccine is highly effective in producing immunity to poliovirus. Because of interference among serotypes during intestinal replication, a single dose of tOPV produces immunity to all three vaccine viruses in approximately 50% of recipients. OPV vaccine produces local intestinal immunity, which reduces

shedding of virus upon re-infection with poliovirus of the same serotype and reduces potential transmission. Subsequent doses cause less interference during intestinal replication and 3 doses produce immunity to all three poliovirus types in more than 95% of recipients in industrialized countries. As with other live-virus vaccines, immunity from oral poliovirus vaccine is probably lifelong.

Contraindications and Precautions to Vaccination

As with other vaccines, a history of a severe allergic reaction (anaphylaxis) to a vaccine component or following a prior dose is a contraindication to further doses. Moderate or severe acute illness (with or without fever) in a patient is considered a precaution to vaccination, although persons with minor illness may be vaccinated.

Since IPV contains trace amounts of streptomycin, neomycin, and polymyxin B, there is a possibility of allergic reactions in persons sensitive to these antibiotics. Persons with allergies that are not anaphylactic, such as skin contact sensitivity, may be vaccinated.

Contraindications to combination vaccines that contain IPV include the contraindications to the individual component vaccines (e.g., DTaP, hepatitis B), but specific ingredients might differ.

Pregnancy

Pregnancy is a precaution to IPV vaccination. Although no adverse effects of IPV vaccine have been documented among pregnant women or their fetuses, vaccination of pregnant women should be avoided on theoretical grounds. However, if a pregnant woman is at increased risk for infection and requires immediate protection against polio, IPV vaccine can be administered in accordance with the recommended schedule for adults.

Poliovirus Vaccine Contraindications and Precautions (IPV)

- Contraindication
  - Severe allergic reaction to a vaccine component or following a prior dose of vaccine
- Precaution
  - Moderate or severe acute illness
  - Pregnancy, unless at increased risk and requiring immediate protection against polio

Vaccine Safety

In pre-licensure trials of enhanced-potency IPV, local reactions were mild and transient. Participants reported induration (18%), pain (13%), and erythema (3.2%) within 48 hours after vaccination. Systemic reactions reported were fever (38% reported temperature ≥ 39°C), irritability, sleepiness, fussiness and crying. Study participants received DTP at the same time as IPV and therefore these systemic reactions could not be attributed to a specific vaccine. However, the frequency and severity of these reactions were comparable to that reported when DTP is given alone.

Poliovirus Vaccine Safety

IPV

- Local reactions mild and transient
- Induration, pain, erythema
  - 3.2%-18%
- Fever (39°C)
  - 38%

OPV

- VAPP occurs very rarely

No increased risks for serious adverse events have been observed in countries relying on all-IPV schedules. After the expanded use of IPV in the United States, a review of the Vaccine Adverse Events Reporting System from 1991 through 1998 did not show an increase in the reporting rate for poliovirus vaccine-associated adverse events with the increased use of IPV. In addition, the distribution of symptoms grouping was comparable for IPV and OPV.

VAPP occurs very rarely after administration of OPV vaccine. The mechanism of VAPP is believed to be a mutation, or reversion, of the attenuated vaccine poliovirus to a more neurotropic form. 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 poliovirus. IPV vaccine does not contain live virus, so it cannot cause VAPP.

The risk of VAPP is 7 to 21 times higher for the first dose than for any other dose in the series. VAPP is more likely to occur in persons age 18 years or older than in children, and it is almost 7,000 times higher for persons with certain types of immunodeficiencies, particularly B-lymphocyte disorders (e.g., agammaglobulinemia and hypogammaglobulinemia), which reduce the synthesis of immune globulins.

VDPVs are genetically divergent forms of vaccine strains. VDPVs develop through prolonged replication of vaccine strains contained in OPV in an immunodeficient individual or in a community with poor vaccination coverage and have re-acquired the neurovirulence and transmissibility of wild poliovirus. The risks of paralysis and manifestations of paralysis caused by VDPVs are similar to those of wild poliovirus of the same serotype. Outbreaks of circulating VDPVs have been responsible for more than 1,200 cases of paralytic polio during 2000–2019 and have exceeded the wild poliovirus case count since 2017.

Vaccine Storage and Handling

IPV vaccine should be maintained at refrigerator temperature between 2°C and 8°C (36°F and 46°F). Manufacturer package inserts contain additional information. For complete information on best practices and recommendations, please refer to CDC's *Vaccine Storage and Handling Toolkit*, www.cdc.gov/vaccines/hcp/admin/storage/toolkit/storage-handling-toolkit.pdf.

Surveillance and Reporting of Poliomyelitis

For information on guidance for state and local health department staff who are involved in surveillance activities for vaccine-preventable diseases, please consult the *Manual for the Surveillance of Vaccine-Preventable Diseases*, www.cdc.gov/vaccines/pubs/surv-manual/chapters.html.

Acknowledgements

The editors would like to acknowledge Valerie Morelli and Ginger Redmon for their contributions to this chapter.

Selected References

CDC. International notes certification of poliomyelitis elimination– the Americas, 1994. *MMWR* 1994;43(39):720 –2.

CDC. Immunization schedules. Atlanta: CDC; 2020. www.cdc.gov/vaccines/schedules/hcp/index.html. Accessed August 29, 2020.

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. Updated recommendations of the Advisory Committee on Immunization Practices (ACIP) regarding routine poliovirus vaccination. *MMWR* 2009;58(30):829–30.

Chard A, Datta S, Tallis G, et al. Progress toward polio eradication - worldwide, January 2018-March 2020. *MMWR* 2020;69(25)784–9.

DeVries A, Harper J, Murray A, et al. Vaccine-derived poliomyelitis 12 years after infection in Minnesota. *N Engl J Med* 2011;364(24):2316–23.

Food and Drug Administration. Prescribing information (package insert). IPOL (poliovirus vaccine inactivated). Silver Spring, MD: U.S. Department of Health and Human Services, Food and Drug Administration; 2019. https://www.fda.gov/media/75695/download. Accessed October 13, 2020.

Global Polio Eradication Initiative. Global wild and circulating vaccine-derived poliovirus cases, 2018-2019 (data as of 24 August 2020). polioeradication.org/polio-today/polio-now/this-week. Accessed August 28, 2020.

Prevots D, Sutter R, Strebel P, et al. Completeness of reporting for paralytic polio, United States, 1980 through 1991. *Arch Pediatr Adolesc Med* 1994;148(5):479–85.

Sutter R, Kew O, Cochi S, et al. Poliovirus vaccine—live. In Plotkin S, Orenstein W, Offit P, eds. Plotkin's *Vaccines*. 7th ed. Philadelphia, PA: Elsevier;2018:866–917.

Vidor E. Poliovirus vaccine—inactivated. In Plotkin S, Orenstein W, Offit P, eds. Plotkin's *Vaccines*. 7th ed. Philadelphia, PA: Elsevier;2018:841–865.

NOTES

NOTES

Wallace G, Curns A, Weldon W, et al. Seroprevalence of poliovirus antibodies in the United States population, 2009–2010. *BMC Public Health* 2016;16:721.

Wattigney W, Mootrey G, Braun M, et al. Surveillances for poliovirus vaccine adverse events, 1991 to 1998: impact of a sequential vaccination schedule of inactivated poliovirus vaccine followed by oral poliovirus vaccine. *Pediatrics* 2001;107(5):E83.

World Health Organization. Polio vaccines: WHO position paper (March, 2016). *Wkly Epidemiol Rec* 2016;91(12):145–68.

Rotavirus

Margaret M. Cortese, MD and Penina Haber, MPH

Diarrheal disease has been recognized in humans since antiquity. Until the early 1970s, a bacterial, viral, or parasitic etiology of diarrheal disease in children could be detected in fewer than 30% of cases. In 1973, Ruth Bishop and colleagues observed a virus particle in the intestinal tissue of children with diarrhea by using electron micrography. This virus was subsequently called "rotavirus" because of its similarity in appearance to a wheel (*rota* is Latin for wheel). By 1980, rotavirus was recognized as the most common cause of severe gastroenteritis in infants and young children in the United States. In the prevaccine era, the majority of children were infected by age 5 years, and rotavirus was responsible for up to 500,000 deaths among children annually worldwide. A vaccine to prevent rotavirus gastroenteritis was first licensed in the United States in 1998 but was withdrawn in 1999 because of its association with intussusception, a type of bowel blockage when the bowel folds into itself like a telescope. Second-generation vaccines were licensed in the United States in 2006 and 2008.

Rotavirus

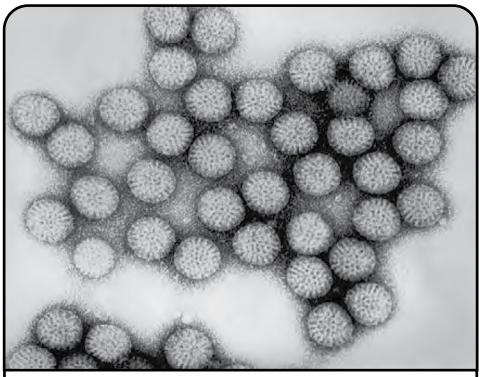
- First identified as cause of diarrhea in 1973
- Most common cause of severe gastroenteritis in infants and children*
- Nearly universal infection by age 5 years*
- Responsible for up to 500,000 diarrheal deaths each year worldwide*

*Prevaccine era

Rotavirus

Rotavirus is a double-stranded RNA virus of the family *Reoviridae*. The virus is composed of three concentric shells that enclose 11 gene segments. The outermost shell contains two important proteins: VP7, or G-protein, and VP4, or P-protein. VP7 and VP4 induce neutralizing antibodies that are believed to be involved in immune protection. From 1996 through 2005, five genotypes of rotavirus (G1P[8], G2P[4], G3P[8], G4P[8] and G9P[8]) accounted for 90% of strains isolated from children younger than age 5 years in the United States. Of these, genotype G1P[8] accounted for more than 75% of strains. In the recent past, G12P[8] has become the most common genotype identified in the United States.

Rotavirus is very stable and may remain viable in the environment for weeks or months if disinfection does not occur.



Rotavirus

- Reovirus (RNA)
- VP7 and VP4 proteins define virus serotype and induce neutralizing antibody
- G1 and G12 strains account for most infections
- Very stable and may remain viable for weeks or months if not disinfected

Pathogenesis

The virus enters the body through the mouth. Viral replication occurs in the villous epithelium of the small intestine. Up to two-thirds of children with severe rotavirus gastroenteritis show the presence of rotavirus antigen in serum (antigenemia) and children can have rotavirus RNA detected in serum.

Infection may result in decreased intestinal absorption of sodium, glucose, and water, and decreased levels of intestinal lactase, alkaline phosphatase, and sucrase activity, and may lead to isotonic diarrhea.

Rotavirus Pathogenesis

- Entry through mouth
- Replication in epithelium of small intestine
- In severe infections – rotavirus antigen detectable in serum
- Infection leads to isotonic diarrhea

The immune correlates of protection from rotavirus are not fully understood. Serum and mucosal antibodies against VP7 and VP4 are probably important for protection from disease. Cell-mediated immunity probably plays a role in protection and in recovery from infection.

Recovery from a first rotavirus infection usually does not lead to permanent immunity. Reinfection can occur at any age. A cohort study in Mexico found that after a single natural infection, 38% of children were protected against any subsequent rotavirus infection, 77% were protected against rotavirus diarrhea, and 87% were protected against severe diarrhea. Subsequent infections conferred progressively greater protection and were generally less severe than the first.

Rotavirus Clinical Features

- Short incubation period (usually less than 48 hours)
- May be asymptomatic or result in severe dehydrating diarrhea with fever and vomiting
- First infection after age 3 months generally most severe
- Gastrointestinal symptoms generally resolve in 3 to 7 days

Clinical Features

The incubation period for rotavirus diarrhea is short, usually less than 48 hours. The clinical manifestations of infection vary and depend on whether it is the first infection or reinfection. Infection may be asymptomatic, may cause self-limited watery diarrhea, or may result in severe dehydrating diarrhea with fever and vomiting. Up to one-third of infected children may have a temperature greater than 39°C (102°F). The first infection after 3 months of age is generally the most severe. The gastrointestinal symptoms generally resolve in 3 to 7 days.

Infants younger than age 3 months have relatively low rates of rotavirus infection, probably because of passive maternal antibody, and possibly because of breastfeeding. Rotavirus infection of adults is usually asymptomatic but may cause diarrheal illness.

The clinical features and stool characteristics of rotavirus diarrhea are nonspecific, and similar illness may be caused by other pathogens. As a result, confirmation of a diarrheal illness as rotavirus requires laboratory testing.

Rotavirus Complications

- Severe diarrhea
- Dehydration
- Electrolyte imbalance
- Metabolic acidosis
- Children who are immunocompromised may have more severe or persistent disease

Complications

Rotavirus infection in infants and young children can lead to severe diarrhea, dehydration, electrolyte imbalance, and metabolic acidosis. Treatment is supportive; feeding should be continued during the illness. Children who are immunocompromised because of congenital immunodeficiency or because of bone marrow or solid organ transplantation may experience severe or prolonged rotavirus gastroenteritis and may have evidence of resulting abnormalities in multiple organ systems, particularly the kidney and liver.

Laboratory Testing

Several commercial test kits are available for testing stool samples that detect a rotavirus antigen (VP6) common to human rotaviruses by enzyme linked immunoassay (EIA). These kits are simple to use, inexpensive, and very sensitive. With the marked reduction in rotavirus disease in children in the United States due to rotavirus vaccination, the positive predictive value of EIA is expected to be lower (and the negative predictive value to be higher) compared with that from the prevaccine era. Multi-pathogen polymerase chain reaction (PCR)-based assays for stool samples that include the ability to detect rotavirus RNA are being increasingly used in clinical laboratories. The clinical interpretation of results from these very sensitive assays may be challenging because detection of nucleic acid of rotavirus or other pathogens in stool may indicate a previous infection and not necessarily the cause of a current illness. Sequence analysis and viral culture are available in research laboratories.

Epidemiology

Occurrence

Rotavirus occurs throughout the world. In the prevaccine era, the proportion of severe diarrhea in children younger than age 5 years that was due to rotavirus was similar (about 35% to 40%) in developed and developing countries, suggesting that improved sanitation alone is not sufficient to prevent infection. The distribution of specific rotavirus genotypes can differ by geographic area and time period.

Reservoir

The reservoir of rotavirus is the gastrointestinal tract and stool of infected humans. Although rotavirus infection occurs in many nonhuman mammals, transmission of animal rotaviruses to humans is believed to be uncommon and probably does not lead to clinical illness. These animal strains are antigenically distinct from those causing human infection, and they rarely cause infection in humans. Although immunocompromised persons may shed rotavirus for a prolonged period, a true carrier state has not been described.

Transmission

Rotaviruses are shed in high concentration in the stool of infected persons. Transmission is by fecal-oral route, both through close person-to-person contact and by fomites (such as toys and other environmental surfaces contaminated by stool). Transmission of rotavirus through contaminated water or food appears to be uncommon.

Rotavirus Epidemiology

- Reservoir
  - Human-GI tract and stool
- Transmission
  - Fecal-oral, person-to-person and fomites
- Temporal pattern
  - Fall and winter (temperate areas)
- Communicability
  - 2 days before onset of diarrhea

Temporal Pattern

In temperate climates, disease is more prevalent during fall and winter. In the United States in the prevaccine era, annual epidemic peaks usually progressed from the Southwest during November and December to the Northeast by April and May. Following vaccine introduction, a biennial pattern of disease activity has emerged with less notable differences in timing by geographic region. In tropical climates, the disease is less seasonal than in temperate areas.

Communicability

Rotavirus is highly communicable, as evidenced by the nearly universal infection of children by age 5 years in the prevaccine era. Infected persons shed large quantities of virus in their stool beginning 2 days before the onset of diarrhea and for several days after the onset of symptoms. Rotavirus may be detected in the stool of immunocompromised persons for more than 30 days after infection. Spread is common within families, institutions, hospitals, and child care settings.

Rotavirus Secular Trends in the United States

Prevaccine era:

- Estimated 2.7 million cases per year
- 95% of children infected by 5 years of age

Following the introduction of rotavirus vaccine:

- Annually averted:
  - 280,000 clinic visits
  - 62,000 emergency department visits
  - 45,000 hospitalizations

Secular Trends in the United States

In the prevaccine era, an estimated 2.7 million rotavirus infections occurred every year in the United States and 95% of children experienced at least one rotavirus infection by age 5 years. Rotavirus infection was responsible for 410,000 physician visits, more than 200,000 emergency department visits, 55,000 to 70,000 hospitalizations, and 20 to 60 deaths annually in children younger than age 5 years. Rotavirus accounted for 30% to 50% of all hospitalizations for gastroenteritis among children younger than age 5 years; the incidence of clinical illness was highest among children age 3 to 35 months.

Rotavirus activity has been monitored through data on routine testing for rotavirus performed at a set of clinical laboratories across the country. A biennial pattern of rotavirus activity emerged after vaccine introduction, with odd numbered years having small, short seasons starting in late winter or early spring and even numbered years having extremely low levels of circulation without a defined season.

The marked reduction in rotavirus disease burden in the United States following the introduction of rotavirus vaccine in 2006 has been documented by data on hospitalizations and emergency department care for diarrhea among young children. An evaluation of claims data of commercially insured children estimated that an average annual 280,000 clinic visits, 62,000 emergency department visits, and 45,000 hospitalizations for rotavirus disease were averted among U.S. children younger than age 5 years during 2007–2011 by routine vaccination. Indirect protection to previously uninfected and

unimmunized children, as well as to some adults, has been described, illustrating the important role that infants play as drivers of rotavirus infection.

Rotavirus vaccination coverage among U.S. children continues to be lower than coverage for other vaccines administered during infancy, in part due to the narrow age restrictions for the doses and particularly the age restriction for completing the series. Among children born during 2015–2016, 73.6% completed the rotavirus vaccine series by age 8 months, the maximum age for the final dose.

Rotavirus Vaccines

In 1998, a rhesus-based tetravalent rotavirus vaccine (RRV-TV [Rotashield]) was licensed and recommended for use in the United States. However, RRV-TV vaccine was withdrawn from the U.S. market within 1 year of its introduction after post-marketing surveillance detected an association with intussusception. The risk of intussusception was most elevated within 3 to 14 days after receipt of the first dose, with a smaller increase in risk within 3 to 14 days after the second dose. Overall, the risk associated with the first dose of RRV-TV vaccine was estimated to be about one case per 10,000 vaccine recipients.

Two live, oral rotavirus vaccines are currently licensed for use, RV5 (RotaTeq) and RV1 (Rotarix) vaccines.

Characteristics

RV5 vaccine contains approximately 2 x 10^6 infectious units of each of the five reassortant strains developed from human and bovine rotavirus strains. RV1 vaccine contains one strain of live, attenuated human strain 89-12 (type G1P1A[8]) rotavirus. Each dose contains at least 10^6 median cell culture infective units of virus. RV1 and RV5 vaccines are administered orally. RV5 and RV1 vaccines contain no adjuvant, antibiotic, or preservative. The RV1 vaccine oral applicator contains latex rubber.

Vaccination Schedule and Use

Rotavirus vaccine is routinely recommended for infants. The vaccine should be administered orally as a series of either two doses (at age 2 and 4 months) for RV1 vaccine or three doses (at age 2, 4, and 6 months) for RV5 vaccine. The vaccination series for both vaccines may be started as early as age 6 weeks. The minimum interval between doses is 4 weeks.

The Advisory Committee on Immunization Practices (ACIP) developed age recommendations that vary from those of the manufacturers. ACIP recommendations state that the maximum age for the first dose of each vaccine is 14 weeks 6 days. The minimum interval between doses of both rotavirus vaccines

Rotavirus Vaccines

- RV5 (RotaTeq)
- RV1 (Rotarix)

Rotavirus Vaccine Characteristics

- RV5 (RotaTeq)
  - Contains five reassortant strains developed from human and bovine parent rotavirus strains
  - Administered orally
- RV1 (Rotarix)
  - Contains one strain of live attenuated human rotavirus (type G1PA[8])
  - Administered orally
  - Oral applicator contains latex rubber

Rotavirus Vaccination Schedule

- Routine vaccination of all infants without a contraindication
- 2-dose series for RV1 vaccine (at age 2 and 4 months)
- 3-dose series for RV5 vaccine (at age 2, 4, and 6 months)
- For both rotavirus vaccines
  - May be started as early as age 6 weeks
  - Maximum age for first dose is 14 weeks 6 days*
  - Minimum interval between doses is 4 weeks
  - Maximum age for any dose is 8 months 0 days*
- ACIP did not define a maximum interval between doses
- No rotavirus vaccine should be administered to infants older than 8 months 0 days*

*Off-label use

Rotavirus Vaccine Recommendations

- Any remaining doses should be administered on schedule
- Complete the series with the same product whenever possible
- If product used for a prior dose or doses is not available or not known, continue or complete the series with the product that is available
- If any dose in the series was RV5 (RotaTeq) or the vaccine brand used for any prior dose is not known, a total of 3 doses of rotavirus vaccine should be administered
- Infants documented to have had rotavirus gastroenteritis before receiving the full course of rotavirus vaccinations should still begin or complete the 2- or 3-dose schedule

Rotavirus Vaccine and Preterm Infants

- ACIP supports vaccination of a preterm infant if:
  - Chronological age is at least 6 weeks
  - Clinically stable
  - Vaccine is administered at time of discharge or after discharge from neonatal intensive care unit or nursery

is 4 weeks. The maximum age for any dose of either rotavirus vaccine is 8 months 0 days. No rotavirus vaccine should be administered to infants older than 8 months 0 days of age. This is an off-label recommendation for both vaccines, because the labeled maximum age for RV1 vaccine is 24 weeks, and the labeled maximum age for RV5 vaccine is 32 weeks.

If any dose in the series was RV5 vaccine or the vaccine brand used for any prior dose in the series is not known, a total of three doses of rotavirus vaccine should be administered.

Rotavirus vaccine should be given at the same visit as other recommended vaccines.

ACIP considers the benefits of rotavirus vaccination of preterm infants to outweigh the risks of adverse events. ACIP supports vaccination of a preterm infant according to the same schedule and precautions as a full-term infant, provided the following conditions are met: the infant's chronological age is at least 6 weeks, the infant is clinically stable, and the vaccine is administered at the time of discharge or after discharge from the neonatal intensive care unit or nursery. The American Academy of Pediatrics will be providing updated guidance on administering vaccine to hospitalized infants in early 2021 through the Red Book.

Breastfeeding does not appear to diminish immune response to rotavirus vaccine. Infants who are being breastfed should be vaccinated on schedule.

Infants documented to have had rotavirus gastroenteritis before receiving the full course of rotavirus vaccination should still begin or complete the 2- or 3-dose series following the age recommendations, as the initial infection may provide only partial protection against subsequent rotavirus disease.

Immunogenicity and Vaccine Efficacy

Phase III clinical efficacy trials of RV5 vaccine were conducted in Finland and United States. The efficacy of the 3-dose series against G1-G4 rotavirus gastroenteritis of any severity was 74%, and against severe G1-G4 rotavirus gastroenteritis was 98% during the first full rotavirus season after vaccination. In a large health care utilization study evaluating children during the first 2 years of life, RV5 vaccine reduced the incidence of office visits for G1-G4 rotavirus gastroenteritis by 86%, emergency department visits for that outcome by 94%, and hospitalizations for that outcome by 96%.

Phase III clinical efficacy trials of RV1 vaccine were conducted in Latin America and Europe. In the Latin American study, the efficacy of the 2-dose series against severe rotavirus gastroenteritis to age 1 year was 85%. In the European study,

the efficacy against severe rotavirus gastroenteritis was 96% through the first rotavirus season, and against any rotavirus gastroenteritis was 87%. Additionally, the efficacy against hospitalization for rotavirus gastroenteritis was 96% through the second season after vaccination.

RV5 vaccine was introduced in the United States in 2006 and RV1 vaccine was introduced in 2008; hence, most early post-introduction data from the United States were based on RV5 vaccine. Several RV5 and RV1 case-control vaccine effectiveness evaluations have been performed in the United States, usually among children younger than age 2 or 3 years. A meta-analysis using data published through 2017 found that the vaccine effectiveness for a full series against the combined outcome of emergency department visit or hospitalization for rotavirus disease was 84% for RV5 vaccine and 83% for RV1 vaccine. Vaccine effectiveness estimates tend to increase with increasing rotavirus disease severity. Both vaccines have demonstrated broad effectiveness across rotavirus genotypes.

The duration of immunity from rotavirus vaccine is not precisely known, although good efficacy has been demonstrated through the first 2 to 3 years of life in the United States. In low-income countries, vaccine effectiveness has generally been lower in the second year of life compared to the first year.

Contraindications and Precautions to Vaccination

As with other vaccines, a history of a severe allergic reaction (anaphylaxis) to a vaccine component or following a prior dose is a contraindication to further doses. Moderate or severe acute illness (with or without fever) in a patient is considered a precaution to vaccination, although persons with minor illness may be vaccinated.

Latex rubber is contained in the RV1 vaccine oral applicator, so infants with a severe allergy to latex should not receive RV1 vaccine. The RV5 vaccine dosing tube is latex free. Some experts prefer that infants with spina bifida or bladder exstrophy, who are at high risk for acquiring latex allergy, receive RV5 vaccine instead of RV1 vaccine to minimize latex exposure in these children.

In response to reported cases of vaccine-acquired rotavirus infection following rotavirus vaccine administration in infants with severe combined immunodeficiency (SCID), ACIP added SCID as a contraindication to rotavirus vaccination. For children with known or suspected immune deficiency, consultation with an immunologist or infectious diseases specialist before administration of rotavirus vaccine should occur. Children who are immunocompromised because of congenital immunodefi-

Rotavirus Vaccine Efficacy

- Any rotavirus gastroenteritis: 74%-87%
- Severe gastroenteritis: 85%-98%
- Both vaccines significantly reduced physician visits for diarrhea, and reduced rotavirus-related hospitalization

Rotavirus Vaccine Contraindications and Precautions

- Contraindication
  - Severe allergic reaction to a vaccine component or following a prior dose of vaccine
  - Latex rubber is contained in the RV1 oral applicator, so infants with a severe allergy to latex should not receive RV1 vaccine; some experts prefer that infants with spina bifida or bladder exstrophy, who are at high risk for acquiring latex allergy, receive RV5 instead of RV1 vaccine
  - History of intussusception
  - Severe combined immunodeficiency (SCID)
- Precaution
  - Moderate or severe acute illnesses, including gastroenteritis (defer until symptoms improve)
  - Altered immunocompetence (SCID is a contraindication)
  - Limited data do not indicate a different safety profile in HIV-infected versus HIV-uninfected infants
  - Chronic gastrointestinal disease (data regarding the safety of rotavirus vaccine for infants with preexisting chronic gastrointestinal conditions are lacking)

ciency, or hematopoietic stem cell or solid organ transplantation, sometimes experience severe, prolonged, and even fatal wild-type rotavirus gastroenteritis.

The limited data available at the time of the ACIP recommendations in 2009 did not indicate that rotavirus vaccines had a substantially different safety profile in human immunodeficiency virus (HIV)-infected infants that are clinically asymptomatic or mildly symptomatic compared with infants that are not HIV infected. Additional data are available from evaluations in HIV-infected infants as well as infants who were HIV exposed but uninfected; rotavirus vaccine was found to be well tolerated and immunogenic.

Post-marketing studies of the currently licensed vaccines have detected an increased risk for intussusception following rotavirus vaccine administration. As a result, a history of intussusception is a contraindication to rotavirus vaccination.

Rotavirus Vaccine - Conditions Not Considered to be Precautions

- Infants living in households with immunocompromised persons
- Infants living in households with pregnant women

Rotavirus vaccine should generally be deferred in infants with acute, moderate or severe gastroenteritis, or other acute illness until the condition improves. However, infants with mild acute gastroenteritis or other mild acute illness can be vaccinated, particularly if a delay in vaccination will postpone the first dose of vaccine beyond 14 weeks 6 days of age. Data regarding the safety of rotavirus vaccine for infants with preexisting chronic gastrointestinal conditions are lacking. Infants with chronic gastrointestinal diseases (e.g., Hirschsprung's disease, short-gut syndrome, or congenital malabsorption syndromes) who are not undergoing immunosuppressive therapy should benefit from rotavirus vaccination.

Infants living in households with persons who are immunocompromised can be vaccinated. The indirect protection for the immunocompromised household member provided by vaccinating the infant in the household outweighs the small risk for transmitting vaccine virus to the immunocompromised household member.

Infants living in households with pregnant women should be vaccinated according to the routine schedule. Because the majority of women of childbearing age have pre-existing immunity to rotavirus, the risk for infection by the attenuated vaccine virus is considered to be very low. It is prudent for all members of the household to employ measures to avoid contact with feces of the vaccinated infant, such as good hand washing after changing a diaper.

Vaccine Safety

In RV5 vaccine clinical trials, detailed information on adverse events were collected in a subset of participants for 42 days after each vaccination. In the first week after any dose, RV5

vaccine recipients had a small but statistically significant increased rate of diarrhea (18.1% in RV5, 15.3% in placebo group) and vomiting (11.6% in RV5, 9.9% in placebo). During the 42-day period following any dose, statistically significantly greater rates of diarrhea, vomiting, otitis media, nasopharyngitis, and bronchospasm occurred in RV5 recipients compared to placebo recipients. The incidence of serious adverse events (including death) within 42 days of any dose was similar among RV5 and placebo recipients. A similar rate of gastroenteritis occurring any time after a dose was reported in both RV5 and placebo recipients (0.2% in RV5, 0.3% in placebo group).

In RV1 clinical trials, participants were monitored for adverse events in the 31-day period after vaccination. During the 31-day period after vaccination, the following unsolicited adverse events occurred at a statistically higher incidence among vaccine recipients: irritability (11.4% in RV1 group, 8.7% in placebo group) and flatulence (2.2% in RV1 group, 1.3% in placebo group). The rate of serious adverse events (including death) was similar in RV1 and placebo recipients. Detailed information on adverse events were collected in a subset of participants during the first week following each dose. Rates of adverse events in this subset were similar in RV1 and placebo recipients except for grade 3 (i.e., those that prevented normal everyday activities) cough or runny nose, which occurred at a slightly but statistically higher rate in the RV1 vaccine group (3.6 %) compared to the placebo group (3.2%).

Post-marketing strain surveillance in the United States and other countries has occasionally detected rotavirus vaccine reassortant strains in stool samples of children with diarrhea. In some of these reports, the reassortant virus seemed to be the likely cause of the diarrheal illness.

Large phase III clinical trials (more than 60,000 infants each) of RV5 and RV1 vaccine evaluated the occurrence of intussusception after vaccination. No increased risk for intussusception was observed for either vaccine. However, post-licensure monitoring was planned to evaluate for a possible risk of intussusception at a lower level than that able to be evaluated in the clinical trials. Post-licensure evaluations of RV5 vaccine and/or RV1 vaccine in some middle and high income countries have identified a low-level increased risk of intussusception following vaccination. In the United States, the risk is estimated as 1 excess case of intussusception per 20,000 to 100,000 vaccinated infants. The risk appears to be primarily during the first week following the first or second dose, but may extend up to 21 days following the first dose. Parents and health care providers should be aware of the low-level increased risk of intussusception following rotavirus vaccine so that infants with possible intussusception can be promptly evaluated.

Rotavirus Vaccine Safety

- RV5
  - Diarrhea 18.1%
  - Vomiting 11.6%
  - Also greater rates of otitis media, nasopharyngitis, and bronchospasm
- RV1
  - Irritability 11.4%
  - Cough or runny nose 3.6%
  - Flatulence 2.2%
- Intussusception
  - Postlicensure-evaluation of RV1 and/or RV5 identified low level risk of intussusception; 1 excess case per 20,000 to 100,000 in the U.S.

Vaccine Storage and Handling

Rotavirus vaccine should be maintained at refrigerator temperature between 2°C and 8°C (36°F and 46°F). Manufacturer package inserts contain additional information, including information on storage of the diluent in oral applicators for RV1. For complete information on best practices and recommendations, please refer to CDC's Vaccine Storage and Handling Toolkit, www.cdc.gov/vaccines/hcp/admin/storage/toolkit/storage-handling-toolkit.pdf.

Surveillance and Reporting of Rotavirus

Rotavirus gastroenteritis is not a nationally notifiable disease in the United States. Estimates of incidence and disease burden are based on special surveys, cohort studies, and hospital discharge data. Methods of surveillance for rotavirus disease at the national level include review of national hospital discharge databases for rotavirus-specific or rotavirus-compatible diagnoses, surveillance for rotavirus disease at sites that participate in the New Vaccine Surveillance Network, and reports of rotavirus detection from a sentinel system of laboratories. Special evaluations (e.g., case control and retrospective cohort methods) have been used to measure the effectiveness of rotavirus vaccine under routine use in the United States. CDC has also established a national strain surveillance system of sentinel laboratories that monitors circulating rotavirus strains. For information on guidance for state and local health department staff who are involved in surveillance activities for vaccine-preventable diseases, please consult the Manual for the Surveillance of Vaccine-Preventable Diseases, www.cdc.gov/vaccines/pubs/surv-manual/chapters.html.

Acknowledgements

The editors would like to acknowledge Valerie Morelli and Ginger Redmon for their contributions to this chapter.

Selected References

American Academy of Pediatrics. Rotavirus infections. In: Kimberlin D, Brady M, Jackson M, et al., eds. Red Book: *2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:700–4.

Baker J, Tate J, Steiner C, et al. Longer-term direct and indirect effects of infant rotavirus vaccination across all ages in the United States in 2000-2013: analysis of a large hospital discharge data set. *Clin Infect Dis* 2019;5;68(6):976–83.

Bowen M, Mijatovic-Rustempasic S, Esona M, et al. Rotavirus strain trends during the postlicensure vaccine era: United States, 2008-2013. *J Infect Dis* 2016;214(5):732–8.

CDC. Addition of history of intussusception as a contraindication for rotavirus vaccination. *MMWR* 2011;60(41):1427.

CDC. Addition of severe combined immunodeficiency as a contraindication for administration of rotavirus vaccine. *MMWR* 2010;59(22):687–8.

CDC. Prevention of rotavirus gastroenteritis among infants and children recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2009;58(No. RR-2):1–25.

Cortes J, Curns A, Tate J, et al. Rotavirus vaccine and health care utilization for diarrhea in U.S. children. *N Engl J Med* 2011;365(12):1108–17

Haber P, Patel M, Pan Y, et al. Intususception after rotavirus vaccines reported to US VAERS, 2006-2012. *Pediatrics* 2013;131(6):1042–9.

Hallowell B, Parashar U, Curns A, et al. Trends in the laboratory detection of rotavirus before and after implementation of routine rotavirus vaccination — United States, 2000–2018. *MMWR* 2019;68(24):539–43.

Leshem E, Moritz R, Curns A, et al. Rotavirus vaccines and health care utilization for diarrhea in the United States (2007-2011). *Pediatrics* 2014;134(1):15–23.

Patel M, Glass R, Desai R, et al. Fulfilling the promise of rotavirus vaccines: how far have we come since licensure? *Lancet Infect Dis* 2012;12(7):561–70 .

NOTES

NOTES

Payne D, Englund J, Weinberg G, et al. Association of rotavirus vaccination with inpatient and emergency department visits among children seeking care for acute gastroenteritis, 2010-2016. *JAMA Netw Open* 2019;2(9):e1912242.

Pindyck T, Tate J, Parashar U. A decade of experience with rotavirus vaccination in the United States - vaccine uptake, effectiveness, and impact. *Expert Rev Vaccines* 2018; 17(7):593–606.

Pringle K, Cardemil C, Pabst L, et al. Uptake of rotavirus vaccine among US infants at Immunization Information System Sentinel Sites. *Vaccine* 2016;34(50):6396–401.

Rha B, Tate J, Weintraub E, et al. Intussusception following rotavirus vaccination: an updated review of the available evidence. *Expert Rev Vaccines.* 2014;13(11):1339–48.

Ruiz-Palacios G, Pérez-Schael I, Velázquez F, et al. Human Rotavirus Vaccine Study Group. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. *N Engl J Med* 2006;354(1):11–22.

Staat M, Payne D, Halasa N, et al. Continued evidence of the impact of rotavirus vaccine in children less than 3 years of age from the US New Vaccine Surveillance Network- a multi-site active surveillance program, 2006-2016. *Clin Infect Dis* 2020;ciaa150. doi: 10.1093/cid/ciaa150. [Epub ahead of print]

Vesikari T, Karvonen A, Prymula R, et al. Efficacy of human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in European infants: randomized, double-blind controlled study. *Lancet* 2007;370(9601):1757–63.

Vesikari T, Matson D, Dennehy P, et al. Safety and efficacy of a pentavalent human–bovine (WC3) reassortant rotavirus vaccine. *N Engl J Med* 2006;354:23–33.

Weintraub E, Baggs J, Duffy J, et al. Risk of intussusception after monovalent rotavirus vaccination. *N Engl J Med* 2014;370(6):513–9.

Yih W, Lieu T, Kulldorff M, et al. Intussusception risk after rotavirus vaccination in U.S. infants. *N Engl J Med* 2014;370(6):503–12

Tatiana Lanzieri, MD; Penina Haber, MPH; Joseph P. Icenogle, PhD, MS; and Manisha Patel, MD, MS

The name rubella is derived from Latin, meaning "little red." Rubella was initially considered to be a variant of measles or scarlet fever. 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, Alfred F. Hess postulated a viral etiology based on his work with monkeys. Following a widespread epidemic of rubella infection in 1940, Norman Gregg, an Australian ophthalmologist, reported in 1941 the occurrence of congenital cataracts among infants born following maternal rubella. This was the first published recognition of congenital rubella syndrome (CRS). Rubella virus was first isolated in 1962 by two independent groups, Paul D. Parkman and colleagues and Thomas H. Weller and Franklin A. Neva. The first rubella vaccines were licensed in 1969. In 1971, a combined measles, mumps, and rubella (MMR) vaccine was licensed for use in the United States. In 2005, a combination measles, mumps, rubella, and varicella (MMRV) vaccine was licensed.

Rubella

- Initially thought to be variant of measles or scarlet fever
- First described as distinct disease in German literature in 1814 (hence "German measles")
- Congenital rubella syndrome (CRS) first described 1941
- Rubella virus isolated in 1962

Rubella Virus

Rubella virus is the sole member of the genus Rubivirus, in the family Matonaviridae. It is an enveloped virus with a single-stranded RNA of positive polarity and has a single antigenic type.

Rubella Virus

- Rubivirus
- RNA virus
- One antigenic type

Pathogenesis

Following respiratory transmission, the virus replicates in the nasopharynx and regional lymph nodes. In a pregnant woman, placental infection occurs during viremia and may lead to transplacental fetal infection. Fetal damage occurs through destruction of cells, as well as disruption of cell division. Fetal infection often results in a persistent infection typically leading to hearing impairment and ocular and cardiovascular abnormalities.

Rubella Pathogenesis

- Respiratory transmission of virus
- Replication in nasopharynx and regional lymph nodes
- Possible transplacental infection of fetus during viremia
  - Hearing impairment and ocular and cardiovascular abnormalities may result

Clinical Features

Acquired Rubella

The average 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 young children, rash is usually the first symptom. In older children and adults, there may be a 1- to 5-day prodrome with low-grade fever, malaise, lymphadenopathy, and upper respiratory symptoms preceding the rash. Lymphadenopathy may begin a week before the rash and last several weeks. The rubella rash

Rubella Clinical Features

- Incubation period 14 days (range, 12 to 23 days)
- Rash first symptom in young children
- Prodrome with low-grade fever, malaise, lymphadenopathy, and upper respiratory symptoms before rash in older children and adults
- Maculopapular rash 14 to 17 days after exposure
- Arthralgia common in adult women

is maculopapular and occurs 14 to 17 days after exposure. The rash usually occurs initially on the face and then progresses from head to foot. It lasts about 3 days and is occasionally pruritic. The rash is fainter than a measles rash, does not coalesce, and is often more prominent after a hot shower or bath. Postauricular, posterior cervical, and suboccipital nodes may be involved.

Arthralgia (joint pain) and arthritis are rare in children and adult males but occur frequently in adult women. Joint symptoms tend to occur at about the same time or shortly after the rash appears and may last for up to 1 month. Fingers, wrists, and knees are often affected. Chronic arthritis is rare. Other symptoms of rubella include conjunctivitis, testalgia, or orchitis. Small, red (Forschheimer) spots may be noted on the soft palate but are not diagnostic for rubella.

Complications

Rubella Complications

- Encephalitis 1 in 6000 cases
- Hemorrhagic manifestations (e.g., thrombocytopenic purpura) 1 in 3000 cases
- Other rare complications—granulomas, orchitis, neuritis, progressive panencephalitis

Complications of rubella are rare. Hemorrhagic manifestations occur in approximately 1 per 3,000 cases. These manifestations may be secondary to low platelets and vascular damage, with thrombocytopenic purpura being the most common. Gastrointestinal, cerebral, or intrarenal hemorrhage may also occur. Effects may last from days to months, and most patients recover. Encephalitis occurs in 1 in 6,000 cases and may be fatal.

Additional rare complications include granulomas in persons with primary immune deficiencies, orchitis, neuritis, and a late syndrome of progressive panencephalitis.

Congenital Rubella Syndrome (CRS)

Congenital Rubella Syndrome (CRS)

- Prevention of CRS is the main objective of rubella vaccination programs
- May lead to miscarriages, stillbirths, and birth defects
- Birth defects may include deafness, eye abnormalities, and congenital heart disease

Prevention of congenital rubella syndrome (CRS) is the main objective of rubella vaccination programs.

Infection with rubella virus is most consequential in early gestation and can lead to miscarriages, stillbirths, and severe birth defects in infants. The risk of CRS is highest when a woman acquires rubella during the first 12 weeks of gestation. Congenital infection with rubella virus can affect many organ systems. Congenital rubella syndrome includes a constellation of birth defects, such as deafness, eye abnormalities (cataracts, glaucoma, retinopathy, microphthalmia), and congenital heart disease.

Laboratory Testing

Many rash illnesses can mimic rubella infection, so clinical diagnosis is unreliable. Acute or recent rubella infection can be confirmed by detection of rubella virus by polymerase chain reaction (PCR), a significant rise in rubella specific immune globulin (Ig)G antibody from paired acute- and convalescent-phase sera, or the presence of rubella-specific IgM antibody.

The optimal time for serum collection for IgM detection is 5 days after onset of symptoms (fever and rash). If serum is collected less than 5 days after onset and is IgM negative, a second sample is necessary to confirm or rule out rubella using IgM detection.

In persons with rubella infection, the virus may be detected in nasal, throat, urine, blood, and cerebrospinal fluid specimens up to 10 days after rash onset (most successful within 3 days). In infants with suspected CRS, nasopharyngeal swabs and/or urine should be collected as close to birth as possible. If CRS is confirmed, infants should be screened for viral shedding monthly after the age of 3 months until two consecutive negative tests are obtained. Viral shedding may be detected for up to one year.

Epidemiology

Occurrence

Rubella used to be a worldwide infection. Endemic rubella and CRS were eliminated in the United States in 2004, and in the region of the Americas in 2009.

Reservoir

Rubella is a human disease. There is no known animal reservoir and no evidence of insect transmission. Infants with CRS may shed rubella virus for an extended period.

Transmission

Rubella is spread from person-to-person via direct contact or droplets shed from the respiratory secretions of infected persons. Rubella may be transmitted by persons with subclinical or asymptomatic cases (up to 50% of all rubella virus infections).

Temporal Pattern

Since rubella elimination in the United States, sporadic cases of rubella have been imported or linked to an imported case, with no temporal pattern.

Communicability

Rubella is most contagious when the rash first appears, but virus may be shed from 7 days before to 7 days after rash onset.

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

Rubella Epidemiology

- Reservoir
  - Human
- Transmission
  - Person-to-person via droplets
- Temporal pattern
  - No known temporal pattern
- Communicability
  - 7 days before to 7 days after rash onset
  - Infants with CRS may shed virus for up to a year

Rubella Secular Trends in the United States

- Following vaccine introduction, incidence declined dramatically
- Postvaccine outbreaks led to recommendations to vaccinate susceptible populations, further decreasing rubella and CRS
- In 2004, endemic rubella declared eliminated in the United States (fewer than 10 cases rubella and 1 case CRS per year)
- Since 2012, all rubella cases imported

Secular Trends in the United States

Rubella and congenital rubella syndrome became nationally notifiable diseases in 1966. Following vaccine introduction in 1969, rubella incidence declined dramatically. Rubella outbreaks continued to occur among adolescents and young adults and in settings where unvaccinated adults gathered. National recommendations to vaccinate susceptible postpubertal females, adolescents, persons in military service, college students, and persons in certain work settings, as well as increased rubella vaccination efforts in the Region of the Americas, led to further declines in rubella and CRS cases. In 2004, endemic rubella was declared eliminated in the United States, with fewer than 10 cases reported annually and less than one CRS case per year. Since 2012, all rubella cases reported in the United States had evidence the patients were infected outside the United States. In most CRS cases reported since 1998, the mother was born outside the United States. Among nine CRS cases reported in the United States between 2004 and 2014, all were import-associated or from unknown sources.

Among children born during 2016–2017, 90.7% received measles, mumps, and rubella-containing vaccine by age 24 months; this was not statistically significantly different from the coverage of 90.3% for children born during 2014–2015.

Rubella Vaccines

- MMR (MMR-II)
- MMRV (ProQuad)

Rubella Vaccines

In 1971, a combined measles, mumps, and rubella (MMR) vaccine was licensed for use in the United States, and the current rubella vaccine component (RA27/3) was licensed in 1979. In 2005, a combination measles, mumps, rubella, and varicella (MMRV) vaccine was licensed.

Rubella vaccine is available as measles, mumps, and rubella vaccine (MMR [MMR-II]) and measles, mumps, rubella, and varicella vaccine (MMRV [ProQuad]). Both MMR and MMRV vaccine contain live, attenuated viruses. Single-antigen rubella vaccine is not available in the United States. The Advisory Committee on Immunization Practices (ACIP) recommends that MMR or MMRV vaccine be used when any of the individual components is indicated.

Rubella Vaccine Characteristics

- Live, attenuated vaccine
- Available as lyophilized powder and reconstituted with sterile, preservative-free water
- Administered by subcutaneous injection
- Contains gelatin
- Contains neomycin

Characteristics

MMR vaccine is a lyophilized preparation of measles virus vaccine live, an attenuated line of measles virus, derived from Enders' attenuated Edmonston strain and propagated in chick embryo cell culture; mumps virus vaccine live, the Jeryl Lynn strain of mumps virus propagated in chick embryo cell culture; and rubella virus vaccine live, the Wistar RA 27/3 strain of live attenuated rubella virus propagated in WI-38 human diploid lung fibroblasts. MMRV vaccine contains measles, mumps, and rubella virus of equal titer and identical to those in the MMR

vaccine. The titer of Oka varicella zoster virus is higher in MMRV vaccine than in single-antigen varicella vaccine, a minimum of 9,772 plaque-forming units (PFU) versus 1,350 PFU, respectively. MMR and MMRV vaccines are supplied as a lyophilized (freeze-dried) powder and are reconstituted with sterile, preservative-free water. Both vaccines contain gelatin. MMR and MMRV vaccines are administered by the subcutaneous route. Each dose of MMR and MMRV vaccine contains neomycin as an antibiotic. It contains no adjuvant or preservative.

Vaccination Schedule and Use

MMR vaccine or MMRV vaccine can be used to implement the vaccination recommendations for prevention of measles, mumps, and rubella. MMR vaccine is licensed for use in persons age 12 months or older. MMRV vaccine is licensed for use in persons age 12 months through 12 years; MMRV vaccine should not be administered to persons age 13 years or older.

Two doses of MMR vaccine, separated by at least 4 weeks, are routinely recommended for children age 12 months or older. Dose 1 of MMR vaccine should be given at age 12 through 15 months. A second dose of MMR vaccine is recommended based on previous observations of the failure of some to generate an immune response to measles following dose 1. Dose 2 is routinely given at age 4 through 6 years, before a child enters kindergarten or first grade. All students entering school should receive 2 doses of MMR vaccine (with the first dose administered at age 12 months or older) before enrollment. Dose 2 of MMR vaccine may be administered as soon as 4 weeks after dose 1.

The minimum interval between doses of MMRV vaccine is 3 months, although when dose 2 is administered 4 weeks following dose 1, it can be considered valid. For the first dose of measles, mumps, rubella, and varicella vaccines at age 12 through 47 months, either separate MMR and varicella (VAR) vaccines, or MMRV vaccine, may be used. However, the risk of febrile seizures is about twice as high for children receiving MMRV vaccine versus separate MMR and VAR vaccines. Providers who are considering administering MMRV should discuss the benefits and risks of both vaccination options with the parents. Unless the parent or caregiver expresses a preference for MMRV, separate MMR vaccine and VAR vaccine should be administered for the first dose in this age group. For the second dose of measles, mumps, rubella, and varicella vaccines at any age and for the first dose at age 48 months or older, the use of MMRV generally is preferred over separate injections of its equivalent component vaccines (i.e., MMR vaccine and VAR vaccine).

Rubella Vaccination Schedule

- 2 dose series at age 12 through 15 months and at age 4 through 6 years
- Minimum age for dose 1 is 12 months
- Minimum interval from dose 1 to 2 is 4 weeks for MMR and 3 months for MMRV (although a 4-week interval is valid)
- Discuss risks and benefits of MMRV versus separate MMR and VAR
  - Separate MMR and VAR vaccines preferred for dose 1 in ages 12 through 47 months
  - MMRV preferred for dose 2 and dose 1 at age 48 months or older

MMR Vaccination of Adults

- Certain persons without acceptable presumptive immunity:
  - At least 1 dose MMR for unvaccinated adults
  - 2 doses MMR for students entering colleges, universities, technical and vocational schools, and other post-high-school educational institutions
  - 2 doses MMR for measles and mumps and at least 1 dose MMR for rubella for healthcare personnel
- Healthcare personnel during an outbreak
  - 2 doses MMR for measles or mumps outbreak and 1 dose MMR for rubella outbreak

Vaccination of Adults

Adults born in 1957 or later should receive at least 1 dose of MMR vaccine unless they have documentation of vaccination with at least 1 dose of measles, mumps, and rubella-containing vaccine or other acceptable presumptive evidence of immunity to these three diseases. Except for health care personnel, who should have documented immunity, birth before 1957 generally can be considered acceptable evidence of immunity to measles, mumps, and rubella.

Colleges and other post-high-school educational institutions are potential high-risk areas for measles, mumps, and rubella transmission because of large concentrations of persons. Prematriculation vaccination requirements for measles immunity have been shown to significantly decrease the risk of measles outbreaks on college campuses where such requirements are implemented and enforced. All students entering colleges, universities, technical and vocational schools, and other institutions for post-high-school education should receive 2 doses of MMR vaccine or have other acceptable evidence of measles, mumps, and rubella immunity before entry.

For unvaccinated health care personnel born before 1957 who lack laboratory evidence of measles, mumps, or rubella immunity or laboratory confirmation of disease, health care facilities should have policies that offer 2 doses of MMR vaccine at the appropriate interval for measles and mumps and 1 dose of MMR vaccine for rubella, respectively. Health care facilities should also have policies for such personnel that recommend 2 doses of MMR vaccine during an outbreak of measles or mumps and 1 dose during an outbreak of rubella. This recommendation is based on serologic studies indicating that among hospital personnel born before 1957, 5% to 10% had no detectable measles, mumps, or rubella antibody. Adequate vaccination for health care personnel born during or after 1957 consists of at least 1 dose of MMR for rubella, and 2 appropriately spaced MMR doses for measles and mumps.

Elimination of indigenous rubella and CRS can be maintained by continuing efforts to vaccinate susceptible adolescents and women of childbearing age, particularly those born outside the United States. These efforts should include vaccinating in family planning clinics and sexually transmitted disease (STD) clinics, and as part of routine gynecologic care. Efforts should also be made to maximize use of premarital serology results when such tests assess rubella immunity; emphasize vaccination for college students; vaccinate women postpartum and postabortion; immunize female prison staff and, when possible, female prison inmates; offer vaccination to at-risk women through the special supplemental program

for Women, Infants, and Children (WIC); and implement vaccination programs in certain workplaces, particularly those employing persons born outside the United States.

Revaccination

Measles-, mumps-, or rubella- virus-containing vaccine administered prior to age 12 months (e.g., for international travel) should not be counted as part of the 2-dose series. Children vaccinated before age 12 months should be revaccinated with 2 doses of appropriately spaced MMR or MMRV vaccine, the first dose administered when the child is age 12 through 15 months (12 months if the child remains in an area where disease risk is high) and the second dose at least 4 weeks later.

Persons who experienced perinatal HIV infection who may have received MMR vaccine prior to the establishment of effective combined antiretroviral therapy (cART), should be revaccinated with 2 appropriately spaced doses of MMR (i.e., the dose does not count) unless they have other acceptable current evidence of immunity. MMR series should be administered once effective cART has been established for at least 6 months and there is no evidence of severe immunosuppression.

Rubella Immunity

Generally, persons can be considered immune to rubella if they were born before 1957, have serologic evidence of rubella immunity (equivocal test results should be considered negative), or laboratory confirmation of disease, or have documentation of adequate vaccination for rubella. Birth before 1957 provides only presumptive evidence of rubella immunity; it does not guarantee that a person is immune to rubella. Birth before 1957 is not acceptable evidence of rubella immunity for women who could become pregnant.

Clinical diagnosis of rubella is unreliable and should not be considered in assessing immune status. Because many rash illnesses may mimic rubella infection and many rubella infections are unrecognized, the only reliable evidence of previous rubella infection is the presence of serum rubella IgG antibody. Laboratories that regularly perform antibody testing are generally the most reliable.

Rubella Immunity

- Born before 1957
  - Not acceptable evidence for women who could become pregnant
- Serologic evidence of rubella immunity (equivocal tests are considered negative)
- Laboratory confirmation of disease
- Documentation of adequate vaccination for rubella

Immunogenicity and Vaccine Efficacy

At least 95% of vaccinated persons age 12 months or older develop serologic evidence of rubella immunity after a single dose, and more than 90% have protection against clinical rubella for at least 15 years. Follow-up studies indicate that 1 dose of vaccine confers long-term, probably lifelong, protection. Seroconversion rates are similar for MMR and MMRV vaccines.

Rubella Vaccine Efficacy

- 95% develop immunity after a single dose
- 1 dose confers long-term, probably lifelong, protection

Although titers to rubella wane in the years after vaccination, there is no evidence that this leads to significant susceptibility to clinical rubella or CRS. Clinical rubella and CRS-affected pregnancies are extremely rare in vaccinated persons the United States.

Rubella Vaccine Contraindications

- Contraindication
  - Severe allergic reaction to vaccine component or following a prior dose
  - Severe immunocompromise
  - Systemic high-dose corticosteroid therapy for 14 days or more
  - HIV infection, regardless of immunocompetence status*
  - Family history of congenital or heredity immunodeficiency in first-degree relatives
  - Pregnancy

*MMRV only

Contraindications and Precautions to Vaccination

As with other vaccines, a history of a severe allergic reaction (anaphylaxis) to a vaccine component or following a prior dose is a contraindication to further doses. Moderate or severe acute illness (with or without fever) in a patient is considered a precaution to vaccination, although persons with minor illness may be vaccinated.

MMR and MMRV vaccines both contain minute amounts of neomycin and gelatin. Persons with alpha-gal allergy may wish to consult their physician before receiving a vaccine that contains gelatin.

Severe immunocompromise (e.g., from hematologic and solid tumors, receipt of chemotherapy, congenital immunodeficiency, long-term immunosuppressive therapy or patients with HIV infection who are severely immunocompromised) is a contraindication for MMR and MMRV vaccination. If the person's level of immunocompetence is uncertain, the decision to vaccinate should be made by the health care provider that prescribed the immunosuppressive medication for those patients whom immunocompromise is due to medication. Patients who have not received chemotherapy for at least 3 months, whose disease remains in remission, and who have restored immunocompetence, may receive MMR or MMRV vaccine. Healthy, susceptible close contacts of severely immunocompromised persons should be vaccinated.

Persons receiving systemic high-dose corticosteroid therapy (2 milligrams per kilogram of body weight or more per day or 20 milligrams or more per day of prednisone) for 14 days or more should not receive MMR or MMRV vaccine because of concern about vaccine safety. MMR or MMRV should not be administered for at least 1 month after cessation of systemic high-dose corticosteroid therapy. Although persons receiving high doses of systemic corticosteroids daily or on alternate days for less than 14 days generally can receive MMR or MMRV immediately after cessation of treatment, some experts prefer waiting until 2 weeks after completion of therapy.

Available data indicate that vaccination with MMR has not been associated with severe or unusual adverse reactions in HIV-infected persons who are not severely immunosuppressed, although antibody responses have been variable. MMR

vaccine is recommended for susceptible HIV-infected persons age 12 months or older with no evidence of current severe immunosuppression ("no evidence of current severe immunosuppression" is defined as CD4 percentages greater than or equal to 15% for 6 months or longer for persons age 5 years or younger; and CD4 percentages greater than or equal to 15% and CD4 count greater than or equal to 200 cells/mm3 for 6 months or longer for persons older than age 5 years). MMR vaccine is not recommended for HIV-infected persons with evidence of severe immunosuppression.

MMRV is not approved for and should not be administered to a person known to be infected with HIV.

A family history of congenital or hereditary immunodeficiency in first-degree relatives (e.g., parents and siblings) is a contraindication for MMR or MMRV vaccine, unless the immune competence of the potential vaccine recipient has been substantiated clinically or verified by a laboratory.

A history of thrombocytopenic purpura or thrombocytopenia is a precaution for MMR and MMRV vaccine. Such persons may be at increased risk for developing clinically significant thrombocytopenia after MMR or MMRV vaccination.

Receipt of specific antiviral drugs (e.g., acyclovir, famciclovir, or valacyclovir) 24 hours before vaccination is a precaution for MMRV vaccine due to the varicella component. These drugs should be avoided for 14 days after vaccination.

Simultaneous use of aspirin or aspirin-containing products is a precaution for MMRV vaccine due to the varicella component. The manufacturer recommends that vaccine recipients avoid the use of salicylates for 6 weeks after receiving MMRV vaccine because of the association between aspirin use and Reye syndrome following chickenpox.

A personal or family (i.e., sibling or parent) history of seizures of any etiology is a precaution for MMRV vaccine but not MMR. Children with a personal or family history of seizures of any etiology should ideally be vaccinated with separate MMR and VAR vaccines because the risks for using MMRV vaccine in this group of children generally outweigh the benefits.

MMR vaccine may be administered to egg-allergic persons without prior routine skin testing or the use of special protocols.

Rubella Vaccine Precautions

- Precaution
  - Moderate or severe acute illness
  - Alpha-gal allergy (consult with physician)
  - Receipt of antibody-containing blood products (wait 3 to 11 months to vaccinate)
  - History of thrombocytopenic purpura or thrombocytopenia
  - Need for tuberculin skin testing or interferon-gamma release assay testing
  - Simultaneous use of aspirin or aspirin-containing products*
  - Personal or family history of seizures of any etiology*
  - Receipt of specific antiviral drugs 24 hours before vaccination*

*MMRV only

Spacing Considerations

The effect of the administration of antibody-containing blood products (e.g., immune globulin, whole blood or packed red blood cells, or intravenous immune globulin) on the response to MMR or MMRV vaccine is unknown. Because of the potential inhibition of the response to vaccination by passively

transferred antibodies, neither MMR vaccine nor MMRV vaccine (nor VAR vaccine) should be administered for 3 to 11 months after receipt of antibody-containing blood products. The interval between the antibody-containing blood product and receipt of MMR or MMRV vaccine is determined by the type of product administered. Antibody-containing products should not be given for 2 weeks following vaccination unless the benefits exceed those of the vaccine. In such cases, vaccine recipients should either be revaccinated later at the appropriate intervals (ranging 3 to 11 months) or tested for immunity and revaccinated if seronegative.

Need for tuberculin skin testing or interferon-gamma release assay (IGRA) testing is a precaution for MMR and MMRV vaccine. Measles vaccine (and possibly mumps, rubella, and varicella vaccines) may transiently suppress the response to tuberculin skin test (TST) in a person infected with Mycobacterium tuberculosis. TST and measles-containing vaccine may be administered at the same visit if necessary. Simultaneously administering TST and measles-containing vaccine does not interfere with reading the TST result at 48 to 72 hours and ensures that the person has received measles vaccine. If the measles-containing vaccine has been administered recently, TST screening should be delayed for at least 4 weeks after vaccination.

Receipt of specific antiviral drugs (e.g., acyclovir, famciclovir, or valacyclovir) 24 hours before vaccination is a precaution for MMRV vaccine due to the varicella component. These drugs should be avoided for 14 days after vaccination.

Vaccination in Pregnancy

Pregnancy is a contraindication for MMR or MMRV vaccine. Pregnancy should be avoided for 4 weeks following MMR or MMRV vaccine. Close contact with a pregnant woman is not a contraindication to MMR or MMRV vaccination of the contact.

If a pregnant woman inadvertently receives MMR or MMRV vaccine, termination of pregnancy is not recommended because the risk to the fetus appears to be extremely low. Instead, individual counseling for these women is recommended. Data from 321 susceptible women who received rubella vaccine showed no evidence of CRS in offspring. Studies conducted in six Latin American countries showed a negligible or absent risk for CRS after administration of rubella vaccine shortly before or during pregnancy. Of the 1,980 susceptible pregnant women followed, 70 (3.6%) of the infants had congenital rubella infection, but none had congenital defects associated with CRS.

Vaccine Safety

Studies have shown MMR and MMRV vaccines are safe and well-tolerated. The National Academy of Medicine, formerly called the Institute of Medicine, reviewed the evidence between MMR vaccination and certain adverse events. The experts determined that evidence supports a causal relation between MMR vaccination and anaphylaxis, febrile seizures, thrombocytopenic purpura, transient arthralgia, and measles inclusion body encephalitis in persons with demonstrated immunodeficiencies.

Most adverse events reported following MMR vaccination (such as fever and rash) are attributable to the measles component. After MMR vaccination, 5% to 15% of susceptible persons develop a temperature of 103°F (39.4°C) or higher, usually occurring 7 to 12 days after vaccination and generally lasting 1 or 2 days. Most persons with fever do not have other symptoms. MMR vaccine is associated with a very small risk of febrile seizures; approximately one case for every 3,000 to 4,000 doses of MMR vaccine administered. The febrile seizures typically occur 6 to 14 days after vaccination and do not appear to be associated with any long-term sequelae. Children with a personal or family history of febrile seizures or family history of epilepsy might be at increased risk for febrile seizures after MMR vaccination.

Allergic reactions following the administration of MMR vaccine are rare. Most of these are minor and consist of a wheal and flare or urticaria at the injection site. Immediate, anaphylactic reactions to MMR vaccine occur in 1.8 to 14.4 cases per million doses.

Arthralgias and other joint symptoms are reported in up to 25% of adult women following MMR vaccine and are associated with the rubella component. Transient lymphadenopathy sometimes occurs following receipt of MMR or other rubella-containing vaccine, and parotitis has been reported rarely (less than 1%) following receipt of MMR or other mumps-containing vaccine.

Rarely, MMR vaccine may cause thrombocytopenia within two months after vaccination. The clinical course of these cases is usually transient and benign, although hemorrhage occurs rarely. Based on case reports, the risk for MMR vaccine-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.

Measles inclusion body encephalitis has been documented after measles vaccination in persons with immune deficiencies. The illness is also known to occur within 1 year after initial infection with wild-type measles virus and has a high death rate. In the cases after MMR vaccination, the time from vaccination to

Rubella Vaccine Safety

MMR

- Fever of 103°F (39.4°C) or higher
  - 5%–15%
- Rash
  - 5%
- Febrile seizures
  - 1 in every 3,000 to 4,000 doses
- Anaphylactic reactions
  - 1.8 to 14.4 cases per million doses
- Arthralgias and other joint symptoms
  - 25% (adult women)

MMRV

- Fever of 102°F or higher
  - 21.5%
- Febrile seizures
  - 1 additional per 2,300 to 2,600 children age 12 through 23 months

development of measles inclusion body encephalitis was 4–9 months, consistent with development of measles inclusion body encephalitis after infection with wild-type measles virus.

In MMRV vaccine prelicensure studies conducted among children age 12 to 23 months, fever (reported as abnormal or elevated greater than or equal to 102°F oral equivalent) was observed 5 to 12 days after vaccination in 21.5% of MMRV vaccine recipients compared with 14.9% of MMR vaccine and VAR vaccine recipients. Two postlicensure studies indicated that one additional febrile seizure per 2,300 to 2,600 children age 12 through 23 months occurred 5 to 12 days after the first dose of MMRV vaccine, compared with children who had received the first dose of MMR vaccine and VAR vaccine administered as separate injections at the same visit. Data from postlicensure studies do not suggest that this increased risk exists for children age 4 to 6 years receiving the second dose of MMRV vaccine.

Multiple studies, as well as a National Academy of Medicine Vaccine Safety Review, refute a causal relationship between autism and MMR vaccine or between inflammatory bowel disease and MMR vaccine.

Vaccine Storage and Handling

For MMR-II and Proquad storage and handling specifics, refer to the manufacturer. For complete information on storage and handling best practices and recommendations, please refer to CDC's Vaccine Storage and Handling Toolkit, https://www.cdc.gov/vaccines/hcp/admin/storage/toolkit/storage-handling-toolkit.pdf.

Surveillance and Reporting for Rubella

Rubella and congenital rubella syndrome became nationally notifiable diseases in 1966. For information on guidance for state and local health department staff who are involved in surveillance activities for vaccine-preventable diseases, please consult the Manual for the Surveillance of Vaccine-Preventable Diseases, www.cdc.gov/vaccines/pubs/surv-manual/chapters.html.

Acknowledgements

The editors would like to acknowledge Zaney Leroy, Ginger Redmon, and Greg Wallace for their contributions to this chapter.

Selected References

American Academy of Pediatrics. Rubella. In: Kimberlin D, Brady M, Jackson M, et al., eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics;2018:705–11.

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(No. RR-12):1–23.

CDC. Immunization of health-care personnel. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2011;60(RR-7):1–45.

CDC. Notice to readers. Revised ACIP recommendations for avoiding pregnancy after receiving rubella-containing vaccine. *MMWR* 2001;50(49):1117.

CDC. Prevention of measles, rubella, congenital rubella syndrome, and mumps, 2013: summary recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2013;62(No. RR-4):1–34.

CDC. Rubella vaccination during pregnancy—United States, 1971–1988. *MMWR* 1989;38(17):289–93.

CDC. Use of combination measles, mumps, rubella, and varicella vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP*). MMWR* 2010;59(No. RR-3):1–12.

Frenkel L, Nielsen K, Garakian A, et al. 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.

Lanzieri T, Redd S, Abernathy E, et al. Rubella. In Roush S, Baldy L, Kirkconnell Hall M, eds. *CDC Manual for the Surveillance of Vaccine-Preventable Diseases*. Atlanta, GA: US Department of Health and Human Services, CDC; 2018.

Mellinger A, Cragan J, Atkinson W, et al. High incidence of congenital rubella syndrome after a rubella outbreak. *Pediatr Infect Dis J* 1995;14(7):573–8.

NOTES

NOTES

Orenstein W, Hadler S, Wharton M. Trends in vaccine-preventable diseases. *Semin Pediatr Infect Dis* 1997;8(1):23–33.

Parkman P, Buescher E, Artenstein M. Recovery of rubella virus from army recruits. *Proc Soc Exp Biol Med* 1962:111;225–30.

Reef S, Frey T, Theall K, et al. The changing epidemiology of rubella in the 1990s. *JAMA* 2002;287(4):464–72.

Stratton K, Ford A, Rusch E, eds. Institute of Medicine. *Adverse Events of Vaccines: Evidence and Causality*. Washington D.C.: The National Academies Press, 2011.

Toizumi M, Motomura H, Vo H, et al. Mortality Associated with Pulmonary Hypertension in Congenital Rubella Syndrome. *Pediatrics* 2014;134(2):e519–26.

Weller T, Neva F. Propagation in tissue culture of cytopathic agents from patients with rubella-like illness. *Proc Soc Exp Biol Med* 1962:111(1);215–25.

Tejpratap S.P. Tiwari, MD; Pedro L. Moro, MD, MPH; and Anna M. Acosta, MD

Tetanus is an acute, often fatal, disease caused by an exotoxin produced by the bacterium *Clostridium tetani*. It is characterized by generalized rigidity and convulsive spasms of skeletal muscles. The muscle stiffness usually begins in the jaw (lockjaw) and neck and then becomes generalized.

Although records from antiquity (5th century BCE) contain clinical descriptions of tetanus, it was in 1884 when tetanus was first produced in animals by injecting them with pus from a fatal human tetanus case. During the same year, tetanus was produced in animals by injecting them with samples of soil. In 1889, Kitasato Shibasaburo isolated the organism from a human, showed that it produced disease when injected into animals, and reported that the toxin could be neutralized by specific antibodies. In 1897, Edmond Nocard demonstrated the protective effect of passively transferred antitoxin, and passive immunization in humans was used for treatment and prophylaxis during World War I. A method for inactivating tetanus toxin with formaldehyde was developed in the early 1920s. This led to the development of tetanus toxoid in 1924. It was first widely used during World War II.

Tetanus

- Caused by exotoxin produced by bacterium *Clostridium tetani*
- Characterized by generalized rigidity and convulsive spasms
- First produced in animals in 1884
- Organism isolated in 1889
- Tetanus toxoid developed in 1924 and widely used during World War II

Clostridium tetani

The *C. tetani* bacterium is a spore-forming, gram-positive, slender, anaerobic rod. The organism is sensitive to heat and cannot survive in the presence of oxygen. The spores, in contrast, are extremely resistant to heat and the usual antiseptics. They can survive autoclaving at 249.8°F (121°C) for 10 to 15 minutes. The spores are also relatively resistant to phenol and other chemical agents.

The spores are widely distributed in soil and in the intestines and feces of horses, sheep, cattle, dogs, cats, rats, guinea pigs, and chickens. Manure-treated soil may contain large numbers of spores. In agricultural areas, a significant number of human adults may harbor the organism. The spores can also be found on skin surfaces and in contaminated heroin.

C. tetani produces two exotoxins, tetanolysin and tetanospasmin. Tetanospasmin is a neurotoxin and causes the clinical manifestations of tetanus. On the basis of weight, tetanospasmin is one of the most potent toxins known: the estimated minimum human lethal dose is 2.5 nanograms per kilogram of body weight (a nanogram is one billionth of a gram) or 175 nanograms for a 70-kg (154-lb) human.

Clostridium tetani

- Anaerobic gram-positive, spore-forming bacteria
- Spores found in soil and intestines and feces of some animals
- Spores resistant to heat and antiseptics
- Two exotoxins produced with growth of bacteria

Tetanus Pathogenesis

- Enters body through wound
- Spores germinate in anaerobic conditions
- 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, 1 to 21 days)
- Three forms: Generalized (most common), local (uncommon), cephalic (rare)
- Generalized tetanus: Trismus (lockjaw), stiffness of the neck, difficulty swallowing, rigidity of abdominal muscles
  - Spasms continue for 3 to 4 weeks
  - Complete recovery may take months

Pathogenesis

C. tetani usually enters the body through a wound. In the presence of anaerobic conditions, the spores germinate. Toxins are produced and disseminated via blood and lymphatics. Tetanospasmin, also referred to as tetanus toxin, acts at several sites within the central nervous system, including peripheral motor end plates, the spinal cord, and the brain, and in the sympathetic nervous system. The typical clinical manifestations of tetanus are caused when tetanus toxin interferes with the release of neurotransmitters, blocking inhibitor impulses. This leads to unopposed muscle contraction and spasm. Seizures may occur, and the autonomic nervous system may also be affected.

Clinical Features

The incubation period is usually about 8 days, with a usual range of 1 to 21 days. In general, the incubation period is longer the further the injury site is from the central nervous system. Shorter incubation periods are also associated with severe disease and a higher chance of death.

On the basis of clinical findings, three different forms of tetanus have been described. The most common type (more than 80% of reported cases) is generalized tetanus. The disease usually presents with a descending pattern. The first sign is trismus, or lockjaw, followed by stiffness of the neck, difficulty in swallowing, and rigidity of abdominal muscles. Other symptoms include elevated temperature, sweating, elevated blood pressure, and episodic rapid heart rate. Spasms may occur frequently and last for several minutes. Spasms continue for 3 to 4 weeks. Complete recovery may take months.

Localized 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. Localized tetanus may precede the onset of generalized tetanus but is generally milder.

Cephalic tetanus is a rare form of the disease, occasionally occurring with otitis media 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.

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. In neonatal tetanus, symptoms usually appear from 4 to 14 days after birth, averaging about 7 days.

Complications

Laryngospasm 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 or an abnormal heart rhythm.

Nosocomial infections are common because of prolonged hospitalization. Secondary infections may include sepsis from indwelling catheters, hospital-acquired pneumonias, and decubitus ulcers. Pulmonary embolism is particularly a problem in persons who use drugs and elderly patients. Aspiration pneumonia is a common late complication of tetanus, found in 50% to 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 or older and unvaccinated persons. In about 20% of tetanus deaths, no obvious pathology is identified and death is attributed to the direct effects of tetanus toxin.

Tetanus Complications

- Laryngospasm
- Fractures
- Hypertension and/or abnormal heart rhythm
- Nosocomial infections
- Pulmonary embolism
- Aspiration pneumonia
- Death

Laboratory Testing

The diagnosis of tetanus is entirely clinical and does not depend upon bacteriologic confirmation. *C. tetani* is recovered from the wound in only 30% of cases and can be isolated from patients who do not have tetanus. Laboratory identification of the organism depends most importantly on the demonstration of toxin production in mice.

Medical Management

All wounds should be cleaned. Necrotic tissue and foreign material should be removed. If tetanic spasms are occurring, supportive therapy and maintenance of an adequate airway are critical.

Tetanus immune globulin (TIG) is recommended for persons with tetanus. TIG can only help remove unbound tetanus toxin. It cannot affect toxin bound to nerve endings. A single intramuscular dose of 500 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.

Because of the extreme potency of the toxin, tetanus disease does not result in tetanus immunity. Active immunization with tetanus toxoid should begin or continue as soon as the person's condition has stabilized.

Antibiotic prophylaxis against tetanus is neither practical nor useful in managing wounds; 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. 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 fewer than 3 prior doses of tetanus toxoid or have an unknown history of prior doses, should receive TIG as well as tetanus toxoid vaccine. This is because early doses of toxoid may prime the immune system but not induce immunity. 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.

Guide to Tetanus Prophylaxis with TIG in Routine Wound Management

History of adsorbed tetanus toxoid-containing vaccines (doses)	Clean, minor wounds DTaP, Tdap or Td[†]	Clean, minor wounds TIG[‡]	All other wounds* DTaP, Tdap or Td[†]	All other wounds* TIG[§]
Unknown or < 3 doses	Yes	No	Yes	Yes
≥3	No[¶]	No	No**	No

*Such as, but not limited to, wounds contaminated with dirt, feces, soil, or saliva; puncture wounds; avulsions; and wounds resulting from missiles, crushing, burns, and frostbite.

†DTaP is recommended for children younger than age 7 years. Tdap is preferred to Td for persons age 11 years or older who have not previously received Tdap. Persons age 7 years or older who are not fully immunized against pertussis, tetanus, or diphtheria should receive one dose of Tdap (preferably the first) for wound management and as part of the catch-up series; if additional tetanus toxoid-containing doses are required, either Td or Tdap vaccine can be used.

§People with HIV infection or severe immunodeficiency who have contaminated wounds (including minor wounds) should also receive TIG, regardless of their history of tetanus immunizations.

¶Yes, if ≥10 years since the last tetanus toxoid-containing vaccine dose.

**Yes, if ≥5 years since the last tetanus toxoid-containing vaccine dose.

Tetanus Epidemiology

- Reservoir
  - Soil and intestine of animals and humans
- Transmission
  - Contaminated wounds
- Temporal pattern
  - Temperate climate: Peaks in summer
  - Tropical climate: Year-round, but may rise during wet seasons
- Communicability
  - Not contagious

Epidemiology

Occurrence

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

Reservoir

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

Transmission

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

Temporal Pattern

In temperate climates, tetanus peaks in the summer. In tropical climates, tetanus generally occurs year round, but may rise during the wet season in some areas.

Communicability

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

Secular Trends in the United States

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

After the 1940s, reported tetanus incidence rates declined steadily. Since the mid-1970s, about 50 to 100 cases (approximately 0.05 cases per 100,000) have been reported annually in the United States. More recently, from 2009–2018, an average of 29 (range 18–37) cases were reported per year. Of the 297 cases reported during this 10-year timeframe, there were 19 deaths, all in adults age 55 years or older. In 2018, 23 tetanus cases were reported, with no deaths.

Among children born during 2016–2017, 93.3% had received at least 3 doses of DTaP vaccine by age 24 months, and 80.6% had received at least 4 doses of DTaP vaccine by age 24 months. Tdap coverage among adolescents age 13 through 17 years reached 90.2% in 2019. Coverage with tetanus toxoid vaccines among adults is lower; the estimates for any dose of a tetanus toxoid-containing vaccine (Td or Tdap) among adults was 63.4% in 2017.

Tetanus Secular Trends in the United States

- 500-600 cases annually before vaccine
- Since the mid-1970s, ~50-100 cases annually
- In 2018, 23 cases were reported with no deaths

Tetanus Toxoid-containing Vaccines

Tetanus toxoid is combined with diphtheria toxoid as diphtheria and tetanus toxoid (DT) vaccine or tetanus and diphtheria toxoid (Td [Tenivac and Tdvax]) vaccine. Tetanus toxoid is also combined with both diphtheria toxoid and acellular pertussis vaccine as DTaP (Infanrix and Daptacel) or Tdap (Boostrix and Adacel) vaccines. Td contains reduced amounts of diphtheria toxoid compared with DT. DTaP and Tdap contain the same pertussis components, but Tdap contains a reduced quantity of some pertussis antigens and diphtheria toxoid. Boostrix contains a reduced quantity of tetanus toxoid compared to Infanrix.

Tetanus Toxoid-containing Vaccines

- DT
- DTaP (Daptacel and Infanrix)
- Td (Tdvax and Tenivac)
- Tdap (Adacel and Boostrix)
- DTaP-HepB-IPV (Pediarix)
- DTaP-IPV/Hib (Pentacel)
- DTaP-IPV (Kinrix and Quadracel)
- DTaP-IPV-Hib-HepB (Vaxelis)

Children younger than age 7 years should receive DTaP vaccine or DT vaccine (in instances where the pertussis vaccine component is contraindicated or where the physician decides that pertussis vaccine is not to be administered). Persons age 7 years or older should receive Td vaccine or Tdap vaccine, even if they have not completed a series of DTaP or DT (Tdap would be off-label for children age 7 through 9 years, but is still recommended by ACIP). Tdap (Boostrix) is approved for persons age 10 years or older; Tdap (Adacel) is approved for persons age 10 through 64 years. DTP vaccines are combined diphtheria and tetanus toxoids and whole cell pertussis vaccine, but none are currently licensed in the United States.

There are five combination vaccines that contain DTaP vaccine. DTaP-HepB-IPV (Pediarix) is licensed for the first 3 doses of the DTaP series among children age 6 weeks through 6 years. DTaP-IPV/Hib (Pentacel) is licensed for the first 4 doses of the component vaccines among children age 6 weeks through 4 years. DTaP-IPV (Kinrix) is licensed only for the fifth dose of DTaP and fourth dose of IPV among children age 4 through 6 years. DTaP-IPV (Quadracel) is licensed only for the fourth dose of DTaP and fourth or fifth dose of IPV among children age 4 through 6 years. DTaP-IPV-Hib-HepB (Vaxelis) is licensed for use in children age 6 weeks through 4 years.

Tetanus Toxoid-containing Vaccine Characteristics

- Administered by intramuscular injection
- Contains aluminum as an adjuvant

Tetanus Toxoid-containing Vaccination Schedule

- DTaP
  - 3-dose primary series at age 2, 4, and 6 months
  - Primary series interval of 4- to 8-weeks and minimum interval 4 weeks
  - Boosters at age 15 through 18 months and age 4 through 6 years
  - Minimum interval for dose 4 is 6 months from dose 3 and minimum age is 12 months
  - If dose 4 is given on or after 4th birthday, the 5th dose is optional
  - DT is used in place of DTaP if child has a valid contraindication to pertussis vaccine

Characteristics

Tetanus toxoid-containing vaccines are administered by intramuscular injection. Each dose of tetanus toxoid-containing vaccines contains aluminum as an adjuvant but no preservative. DTaP-HepB-IPV (Pediarix), DTaP-IPV/Hib (Pentacel), DTaP-IPV-Hib-HepB (Vaxelis), DTaP-IPV (Kinrix), and DTaP-IPV (Quadracel) contain neomycin and polymyxin B as antibiotics. DTaP-IPV-Hib-HepB (Vaxelis) contains streptomycin as an antibiotic. DTaP-HepB-IPV (Pediarix) and DTaP-IPV-Hib-HepB (Vaxelis) vaccines contain yeast protein. Presentations of some tetanus toxoid-containing vaccines contain latex rubber.

Vaccination Schedule and Use

DTaP (Infanrix and Daptacel)

DTaP (diphtheria, tetanus toxoids, and acellular pertussis vaccine) is recommended for children age 6 weeks through 6 years. The routine schedule is a primary series of 3 doses at age 2, 4, and 6 months, a booster dose between age 15 through 18 months, and another booster dose between age 4 through 6 years (total of 5 doses). The first 3 doses should be given at 4- to 8-week intervals (minimum of 4 weeks). Dose 4 should follow dose 3 by no less than 6 months and should not be administered before age 12 months.

Dose 4 of both brands of DTaP is recommended to be administered at age 15 through 18 months (15 through 20 months for Daptacel). Dose 4 may be given as early as age 12 months if at least 6 months have elapsed since dose 3 and, in the opinion of the vaccine provider, the child is unlikely to return for an additional visit between age 15 through 18 months.

Children who received 4 doses before their fourth birthday should receive a fifth dose of DTaP before entering school. The fifth dose is not necessary (but may be given) if dose 4 in the series was given on or after the fourth birthday. Administering the fifth dose increases antibody levels and may decrease the risk of school-age children transmitting the disease to younger siblings who are not fully vaccinated.

If a child has a valid contraindication to pertussis vaccine, DT should be used to complete the vaccination series. If the child was younger than age 12 months when the first dose of DT was administered (as DTP, DTaP, or DT), the child should receive a total of 4 DT doses. If the child was age 12 months or older at the time the first dose of DT was administered, 3 doses (with dose 3 administered 6 through 12 months after dose 2) will complete the primary DT series. If dose 4 of DTP, DTaP, or DT is administered before the fourth birthday, a fifth dose is recommended at age 4 through 6 years.

DTaP-HepB-IPV (Pediarix)

DTaP-HepB-IPV vaccine is approved for use as a 3-dose series for children age 6 weeks through 6 years. It is administered to infants at age 2, 4, and 6 months. The minimum intervals for DTaP-HepB-IPV vaccine are determined by the DTaP component. The 3 doses must be separated by at least 4 weeks between doses. Because the minimum age for the first dose of DTaP-HepB-IPV vaccine is 6 weeks, this vaccine cannot be used for the birth dose of hepatitis B (HepB) vaccine. The final dose of DTaP-HepB-IPV vaccine should be administered at age 24 weeks or older, the minimum age for completion of the hepatitis B vaccine series. When DTaP-HepB-IPV vaccine is used to provide 3 doses at age 2, 4, and 6 months (based on the DTaP and IPV schedules), this will result in a 4-dose HepB vaccine series, which is acceptable.

DTaP-IPV/Hib (Pentacel)

DTaP-IPV/Hib vaccine is approved for use as a 4-dose series for children age 6 weeks through 4 years. It is administered to infants at age 2, 4, 6, and 15 through 18 months. The minimum intervals for DTaP-IPV/Hib vaccine are determined by the DTaP component. The first 3 doses must be separated by at least 4 weeks between doses. Dose 4 must be separated from dose 3 by at least 6 months, and should not be administered before age 12 months. When DTaP-IPV/Hib vaccine is used

to provide 4 doses at age 2, 4, 6, and between 15 through 18 months (based on the DTaP and Hib schedules), an additional booster dose with IPV-stand alone or DTaP-IPV vaccine should be administered at age 4 through 6 years. This will result in a 5-dose IPV vaccine series, which is acceptable.

DTaP-IPV-Hib-HepB (Vaxelis)

DTaP-IPV-Hib-HepB is approved for use as a 3-dose series for children age 6 weeks through 4 years. It is administered to infants at age 2, 4, and 6 months. The minimum intervals for DTaP-IPV-Hib-HepB vaccine are determined by the DTaP component. The 3 doses must be separated by at least 4 weeks between doses. Because the minimum age for the first dose of DTaP-IPV-Hib-HepB vaccine is 6 weeks, this vaccine cannot be used for the birth dose of hepatitis B (HepB) vaccine. The final dose of DTaP-IPV-Hib-HepB vaccine should be administered at age 24 weeks or older, the minimum age for completion of the hepatitis B vaccine series. When DTaP-IPV-Hib-HepB vaccine is used to provide 3 doses at age 2, 4, and 6 months (based on the DTaP and IPV schedules), this will result in a 4-dose HepB vaccine series, which is acceptable.

DTaP-IPV (Kinrix)

DTaP-IPV (Kinrix) vaccine is approved only for dose 5 of DTaP vaccine and dose 4 of IPV vaccine in children age 4 through 6 years whose previous DTaP vaccine doses have been with Infanrix and/or Pediarix for dose 1, 2, and 3 and Infanrix for dose 4. However, if DTaP-IPV (Kinrix) vaccine is administered to children who received another brand of DTaP vaccine for prior DTaP vaccine doses, or if administered as dose 1, 2, 3, or 4 of the DTaP vaccine series or dose 1, 2, or 3 of the IPV vaccine series, the dose of DTaP-IPV (Kinrix) does not need to be repeated.

DTaP-IPV (Quadracel)

DTaP-IPV (Quadracel) vaccine is approved only for dose 5 of DTaP vaccine and dose 4 or 5 of IPV vaccine in children age 4 through 6 years who have received 4 doses of Pentacel and/or Daptacel vaccine. However, if DTaP-IPV (Quadracel) vaccine is administered to children who received another brand of DTaP vaccine for prior DTaP vaccines doses, or if administered as dose 1, 2, 3, or 4 of the DTaP vaccine series or dose 1, 2, or 3 of the IPV series, the dose of DTaP-IPV (Quadracel) does not need to be repeated.

Tdap (Boostrix and Adacel) and Td (Tenivac and Tdvax)

Both Tdap vaccines are approved by the FDA for a booster dose for persons who have completed the recommended childhood DTP/DTaP vaccination series. Boostrix is approved for persons age 10 years or older. Adacel is approved for a single dose in persons age 10 through 64 years. A second dose of Adacel is also licensed for administration 8 or more years

Tetanus Toxoid-containing Vaccination Schedule

- Tdap
  - 1 dose at age 11 through 18 for adolescents who have completed DTaP series
  - Booster dose of Td or Tdap every 10 years for all persons

after the first Tdap dose and for use for tetanus prophylaxis when indicated for wound management if at least 5 years have elapsed since the previous receipt of any tetanus toxoid-containing vaccine. Both Td vaccines are approved for use in persons age 7 years or older.

A single Tdap dose is recommended for adolescents age 11 through 18 years who have completed the recommended childhood DTP/DTaP vaccination series, preferably at age 11 through 12 years. Adults age 19 years or older who have not previously received Tdap should receive a single dose of Tdap. To reduce the burden of pertussis in infants, a dose of Tdap has been recommended during each pregnancy since 2012, although this practice is an off-label use.

All adolescents and adults should have received a primary series of at least 3 documented doses of tetanus and diphtheria toxoids-containing vaccine (i.e., DTaP, DTP, DT, or Td) during their lifetime. A person without such documentation should receive a series of 3 doses of tetanus- and diphtheria-containing vaccine. One of these doses, preferably the first, should be Tdap. The remaining 2 doses should be either Td or Tdap.

For persons age 7 to 9 years who receive a dose of Tdap as part of the catch-up series, an adolescent Tdap dose should be administered at age 11 through 12 years. If a Tdap dose is administered at age 10 years or older, the Tdap dose may count as the adolescent Tdap dose. Either brand of Tdap may be used.

Adults age 19 years or older who previously have not received Tdap should receive a single dose of Tdap to protect against pertussis and reduce the likelihood of transmission. For adults age 19 through 64 years, either brand of Tdap may be used. Adults age 65 years or older should be vaccinated with Boostrix, if feasible. However, either vaccine administered to a person age 65 years or older is immunogenic and would provide protection. A dose of either vaccine would be considered valid.

Adolescents and adults who have not previously received Tdap, and have or anticipate having close contact with an infant younger than age 12 months (e.g., parents, siblings, grandparents, child care providers, and health care personnel) should receive a single dose of Tdap to protect against pertussis. Ideally, these persons should receive Tdap at least 2 weeks before beginning close contact with the infant.

Health care personnel should receive a single dose of Tdap as soon as feasible if they have not previously received Tdap, regardless of the time since their most recent Td vaccination.

When Tdap is indicated (e.g., routine vaccination, catch-up vaccination, or pregnancy), it can be administered regardless of the interval since the last tetanus- or diphtheria-toxoid-

Use of Tdap

- 1 dose Tdap during each pregnancy (off-label use)
- 1 dose Tdap for the following with no previous documentation of Tdap: adults, adolescents and adults who have or anticipate having close contact with an infant younger than age 12 months, and health care personnel
- 3 doses of tetanus- and diphtheria-containing vaccine (1 dose should be Tdap) for adolescents and adults without documentation of a primary series

containing vaccine. After receipt of Tdap, persons should continue to receive a dose of Td or Tdap for routine booster immunization against tetanus and diphtheria every 10 years unless needed sooner for tetanus prophylaxis as part of wound management.

Vaccination during Pregnancy

Pregnant women who have completed the childhood immunization schedule and were last vaccinated greater than 10 years previously should receive a booster dose of tetanus toxoid–containing vaccine to prevent neonatal tetanus. The risk for neonatal tetanus is minimal if a previously unvaccinated woman has received at least 2 properly spaced doses of a tetanus toxoid–containing vaccine during pregnancy; at least 1 of the doses administered during pregnancy should be Tdap, administered according to published guidance. If more than 1 dose is needed, either Td or Tdap may be used. The 3-dose primary series should be completed at the recommended intervals.

Tetanus Toxoid-containing Vaccine Efficacy

- After valid 3-dose primary series and booster (children) or 3 valid doses (adults), essentially all recipients achieve antitoxin levels great than protective level
- Antitoxin levels decrease with time so boosters are recommended every 10 years
- Small percentage of individuals are unprotected before 10 years, so booster for wound needed if more than 5 years have elapsed since last dose

Immunogenicity and Vaccine Efficacy

After a primary series of 3 properly spaced doses of tetanus toxoid-containing vaccines in infants and a booster at 15 through 18 months of age or 3 properly spaced doses in adults, essentially all recipients achieve antitoxin levels considerably greater than the protective level of 0.1 IU/mL.

Efficacy of the tetanus toxoid has never been studied in a vaccine trial. It can be inferred from protective antitoxin levels that a complete tetanus toxoid series has an efficacy of almost 100%. In the series of 233 cases from 2001–2008, only 7 cases (3%) had received a complete tetanus toxoid series with the last dose within the last 10 years.

Antitoxin levels decrease with time. By 10 years after the last dose, most persons have antitoxin levels that only approach the minimal protective level. As a result, routine boosters are recommended every 10 years.

In a small percentage of individuals, antitoxin levels fall below the minimal protective level before 10 years have elapsed. To ensure adequate protective antitoxin levels, persons who sustain a wound that is other than clean and minor should receive a tetanus booster if more than 5 years have elapsed since their last dose.

Contraindications and Precautions to Vaccination

As with other vaccines, a history of a severe allergic reaction (anaphylaxis) to a vaccine component or following a prior dose is a contraindication to further doses. Moderate or severe

acute illness (with or without fever) in a patient is considered a precaution to vaccination, although persons with minor illness may be vaccinated. If moderate to severe acute illness accompanies a wound that is neither clean nor minor, the risk of withholding tetanus-toxoid vaccine outweighs the risk of administering tetanus-toxoid vaccine, so the vaccine should be given as part of wound management.

Contraindications to combination vaccines that contain DTaP include the contraindications to the individual component vaccines (e.g., IPV, hepatitis B, Hib), but specific ingredients might differ. DTaP-HepB-IPV (Pediarix) and DTaP-IPV-Hib-HepB (Vaxelis) vaccines contain yeast. Presentations of some tetanus toxoid-containing vaccines contain latex rubber. DTaP-HepB-IPV (Pediarix), DTaP-IPV/Hib (Pentacel), DTaP-IPV-Hib-HepB (Vaxelis), DTaP-IPV (Kinrix), and DTaP-IPV (Quadracel) contain neomycin and polymyxin B. DTaP-IPV-Hib-HepB (Vaxelis) contains streptomycin.

Encephalopathy not attributable to another identifiable cause occurring within 7 days after vaccination with DTaP, DTP, or Tdap is a contraindication for DTaP and Tdap vaccination.

A progressive or unstable neurological disorder, uncontrolled seizures, or progressive encephalopathy is a precaution for DTaP and Tdap vaccination. For persons with a known or suspected neurologic condition, vaccination with DTaP or Tdap should be delayed until the condition has been evaluated, treatment initiated, and the condition stabilized. These conditions include the presence of an evolving neurologic disorder (e.g., uncontrolled epilepsy, infantile spasms, and progressive encephalopathy); a history of seizures that has not been evaluated; or a neurologic event that occurs between doses of 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 neither contraindications nor precautions to DTaP or Tdap vaccination.

Guillain-Barré syndrome within 6 weeks after a previous dose of tetanus toxoid-containing vaccine is a precaution for DTaP, Tdap, DT, and Td vaccination.

A history of Arthus-type hypersensitivity reactions after a previous dose of diphtheria toxoid-containing or tetanus toxoid-containing vaccine is a precaution for DTaP, Tdap, DT, and Td vaccination; vaccination should be deferred until at least 10 years have elapsed since the last tetanus toxoid-containing vaccine.

Diphtheria and Tetanus Toxoids-containing Vaccine Contraindications and Precautions

- Contraindication
  - Severe allergic reaction to vaccine component or following a prior dose
  - Encephalopathy not attributable to another identifiable cause within 7 days after vaccination*
- Precaution
  - Moderate or severe acute illness
  - Progressive or unstable neurological disorder*
  - Uncontrolled seizures*
  - Progressive encephalopathy*
  - Guillain-Barré syndrome within 6 weeks after a previous dose of tetanus toxoid-containing vaccine**
  - History of Arthus-type hypersensitivity reactions after a previous dose of diphtheria toxoid- or tetanus toxoid-containing vaccine**

*DTaP and Tdap

**DTaP, DT, Tdap, Td

Tetanus Toxoid-containing Vaccine Safety

DTaP

- Pain, redness, or swelling
  - 20%-40%
  - More frequent after dose 4 or 5
- Temperature of 101°F
  - 3%-5%
- Moderate or severe systemic reactions
  - Fewer than 1 in 10,000 doses
- Arthus-type reactions are rare

Tdap, Td

- Pain, redness, or swelling
  - 21%-75%
- Temperature of 100.4°F or higher
  - 1.1%-5%

Vaccine Safety

DTaP vaccine may cause local reactions, such as pain, redness, or swelling. Local reactions have been reported in 20% to 40% of children after each of the first 3 doses. Local reactions appear to be more frequent after the fourth and/or fifth doses. Mild systemic reactions such as drowsiness, fretfulness, and low-grade fever may also occur. Temperature of 101°F or higher is reported in 3% to 5% of DTaP recipients. These reactions are self-limited and can be managed with symptomatic treatment with acetaminophen or ibuprofen.

Moderate or severe systemic reactions (such as fever of 105°F or higher, febrile seizures, persistent crying lasting 3 hours or longer, and hypotonic-hyporesponsive episodes) have been reported after administration of DTaP, but occur less frequently than among children who received whole-cell DTP. Rates of moderate or severe systemic reactions vary by symptom and vaccine but generally occur in fewer than 1 in 10,000 doses.

Exaggerated local (Arthus-type) reactions are rarely reported but may occur following receipt of a vaccine containing diphtheria or tetanus toxoids.

The most common adverse reaction following vaccination with both brands of Tdap is a local reaction, such as pain (66% to 75%), redness (25%), or swelling (21%) at the site of injection. Temperature of 100.4°F or higher was reported by 1.4% to 5% of Tdap recipients and 1.1% to 5% of Td recipients. Tdap recipients also reported a variety of nonspecific systemic events, such as headache, fatigue and gastrointestinal symptoms.

The Institute of Medicine reported in 2011 that the evidence was inadequate to accept or reject a causal relation between receipt of diphtheria toxoid and tetanus toxoid-containing vaccine and encephalitis, encephalopathy, infantile spasms, seizures, ataxia, autism, acute disseminated encephalomyelitis, transverse myelitis, optic neuritis, onset of multiple sclerosis in adults, relapse of multiple sclerosis in adults, relapse of multiple sclerosis in children, Guillain-Barré syndrome, chronic inflammatory disseminated polyneuropathy, opsoclonus myoclonus syndrome, or Bell's palsy.

The most frequently reported adverse events after DTaP in the Vaccine Adverse Effect Reporting System (VAERS) and Vaccine Safety Datalink (VSD), two post-licensure surveillance systems, were consistent with observations from pre-licensure studies of these vaccines. When VAERS DTaP reports for each vaccine brand were compared individually with reports for all other inactivated vaccines in the VAERS database, no concerning patterns of adverse events were observed.

Routine VAERS surveillance for and VSD studies on adverse events following receipt of Tdap vaccines in persons aged 10 through 64 years have provided reassuring data consistent with the prelicensure clinical trial safety data and have not demonstrated any associations between Tdap and the following rare adverse events: encephalopathy-encephalitis-meningitis, paralytic syndromes,seizures, cranial nerve disorders, and Guillain-Barré syndrome.

Vaccine Storage and Handling

DTaP, Td, and Tdap vaccines should be maintained at refrigerator temperature between 2°C and 8°C (36°F and 46°F). Manufacturer package inserts contain additional information. For complete information on best practices and recommendations, please refer to CDC's Vaccine Storage and Handling Toolkit, www.cdc.gov/vaccines/hcp/admin/storage/toolkit/storage-handling-toolkit.pdf.

Surveillance and Reporting of Tetanus

For information on guidance for state and local health department staff who are involved in surveillance activities for vaccine-preventable diseases, please consult the Manual for the Surveillance of Vaccine-Preventable Diseases, www.cdc.gov/vaccines/pubs/surv-manual/chapters.html

Acknowledgements

The editors would like to acknowledge Susan Hariri, Fiona Havers, and Jennifer Liang for their contributions to this chapter.

Selected References

American Academy of Pediatrics. Tetanus. In: Kimberlin D, Brady M, Jackson M, et al., eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics;2018:793–8.

CDC. Diphtheria, tetanus, and pertussis: Recommendations for vaccine use and other preventive measures. Recommendations of the Immunization Practices Advisory Committee (ACIP). *MMWR* 1991;40(No. RR-10):1–28.

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(No. RR-7):1–25.

NOTES

NOTES

CDC. Preventing tetanus, diphtheria, and pertussis among adolescents: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccines. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2006;55(No. RR-3):1–34.

CDC. Preventing tetanus, diphtheria, and pertussis among adults: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccines. Recommendations of the Advisory Committee on Immunization Practices (ACIP) and Recommendation of ACIP, supported by the Healthcare Infection Control Practices Advisory Committee (HICPAC), for Use of Tdap Among Health-Care Personnel. *MMWR* 2006;55(No. RR-17):1–33.

CDC. Prevention of pertussis, tetanus, and diphtheria with vaccines in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2018;67(RR-2):1–44.

CDC. Updated Recommendations for Use of Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis (Tdap) Vaccine from the Advisory Committee on Immunization Practices, 2010. *MMWR* 2011;60(No.1):13–5.

CDC. Use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccines: updated recommendations of the Advisory Committee on Immunization Practices — United States, 2019. *MMWR* 2020;69(3):77–83.

Pascual F, McGinley E, Zanardi L, et al. Tetanus surveillance—United States, 1998–2000. *MMWR* 2003;52(No. SS-3):1–8.

Roper M, Wassilak S, Scobie H. Tetanus Toxoid. In: Plotkin S, Orenstein W, Offit P, et al., eds. Plotkin's *Vaccines*. 7th ed. Elsevier;2018:1052–79.

Adriana Lopez, MHS; Theresa Harrington, MD, MPH&TM; and Mona Marin, MD

Varicella is an acute infectious disease caused by varicella-zoster virus (VZV). Primary varicella infection (chickenpox) was not reliably distinguished from smallpox until the end of the 19th century. In 1875, Rudolf Steiner demonstrated that chickenpox was caused by an infectious agent by inoculating volunteers with the vesicular fluid from a patient with acute varicella. In 1954, Thomas Weller used cell culture to isolate VZV from vesicular fluid of patients with varicella or zoster. A live, attenuated varicella vaccine was developed in Japan in the 1970s. The vaccine virus was developed from virus isolated by Michiaki Takahashi from vesicular fluid from an otherwise healthy child with varicella disease. Varicella vaccine was licensed for general use in Japan and Korea in 1988, and in the United States in 1995 for persons age 12 months or older. In 2005, a combination measles, mumps, rubella, and varicella (MMRV) vaccine was licensed in the United States for persons age 12 months through 12 years.

Varicella

- Acute infectious disease caused by varicella-zoster virus (VZV)
- Distinguished from smallpox at the end of the 19th century
- Live, attenuated varicella vaccine developed in 1970s
- Varicella and MMRV vaccines licensed for use in the U.S. in 1995 and 2005, respectively

Varicella-Zoster Virus

VZV is a DNA virus and is a member of the herpesvirus group. Like other herpesviruses, VZV persists in the body as a latent infection after the primary (first) infection; VZV persists in sensory nerve ganglia. Primary infection with VZV results in varicella. Latent infection can reactivate resulting in herpes zoster (shingles). The virus has a short survival time in the environment.

Varicella-Zoster Virus (VZV)

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

Pathogenesis

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

Varicella Pathogenesis

- Enters through respiratory tract and conjunctiva
- Replication in nasopharynx and regional lymph nodes
- Primary viremia 4 to 6 days after infection
- Multiple organs infected during viremia
- Secondary viremia with viral skin infection after replication

Clinical Features

The incubation period is 14 to 16 days after exposure, with a range of 10 to 21 days. The incubation period may be prolonged (e.g., up to 28 days or more) in those who have received postexposure prophylaxis with varicella specific immune globulin.

Varicella Clinical Features

- Incubation period 14 to 16 days (range, 10 to 21 days)
- Prolonged incubation period if received postexposure prophylaxis with varicella specific immune globulin

Primary Infection (Varicella)

- Rash often first sign of disease in children; adults may have 1 to 2 days of fever and malaise before rash
- In unvaccinated individuals, generalized and pruritic rash progresses rapidly
- Clinical course in healthy children is mild; adults may have more severe disease
- Recovery usually results in lifetime immunity

Primary Infection (Varicella)

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.

In individuals who have not received varicella vaccine, the rash is generalized and pruritic and progresses rapidly (within 24 hours) from macules to papules to vesicular lesions before crusting. The rash usually appears first on the scalp, face or trunk, and then spreads to the extremities; the highest concentration of lesions is on the trunk. 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 all stages of development at the same time. For example, macular lesions may be observed in the same area of skin as mature vesicles. Healthy children usually have 250 to 500 lesions in 2 to 4 successive crops.

The clinical course in healthy children is generally mild, fever (up to 102°F) and other systemic symptoms (e.g., malaise, headache) usually resolve within 2 to 4 days after onset of the rash. Adults may have more severe disease and have a higher incidence of complications. Immunocompromised children may develop a severe progressive form of varicella characterized by high fever, extensive vesicular eruption, and high complication rates. Persons infected with human immunodeficiency virus (HIV) are also at risk for severe, prolonged illness.

Recovery from primary varicella infection usually results in lifetime immunity. In otherwise healthy persons, a second occurrence of varicella is uncommon; it is more common in immunocompromised persons. As with other viral diseases, re-exposure to natural (wild) varicella may lead to reinfection that boosts antibody titers without causing clinical illness or detectable viremia.

Breakthrough varicella is defined as varicella due to infection with wild-type VZV occurring more than 42 days after varicella vaccination; breakthrough infection can occur after 1 or 2 doses of vaccine. With decreasing incidence of varicella overall and increasing varicella vaccination coverage, more than half of varicella cases reported during the mature phase of the vaccination program are breakthrough varicella cases. Breakthrough varicella is less severe than varicella in unvaccinated persons, with the median number of skin lesions commonly less than 50; vesicular lesions are less common and the lesions are commonly papules that do not progress to vesicles. Varicella in vaccinated persons is

typically shorter in duration and has a lower incidence of fever than in unvaccinated persons. However, about 25% to 30% of breakthrough varicella cases in vaccinees who received one dose have clinical features more similar to those in unvaccinated children, and complications with visceral dissemination, hospitalizations, or death, although uncommon, have been reported.

Complications

Acute varicella is generally mild and self-limited, but it may be associated with complications. Secondary bacterial infections of skin lesions with Staphylococcus or Streptococcus (primarily invasive group A) are the most common cause of hospitalization and outpatient medical visits and can lead to death. Pneumonia following varicella is usually viral but may be bacterial. Primary viral pneumonia is uncommon among immunocompetent children but is the most common complication in adults. Secondary bacterial pneumonia is more common in children younger than age 1 year. Central nervous system manifestations of varicella range from aseptic meningitis to encephalitis. Encephalitis is an infrequent complication of varicella (1 per 50,000 cases of varicella in unvaccinated children) and may lead to seizures and coma. Diffuse cerebral involvement is more common in adults than in children. Involvement of the cerebellum, with resulting cerebellar ataxia, is the most common central nervous system manifestation (1 per 4,000 cases of varicella in unvaccinated children) and generally has a good outcome. Reye syndrome may follow varicella, although this outcome has become very rare with the recommendation to not use aspirin or other salicylates to reduce fever in children with varicella. Rare complications of varicella include aseptic meningitis, transverse myelitis, Guillain-Barré syndrome, thrombocytopenia, hemorrhagic varicella, purpura fulminans, glomerulonephritis, myocarditis, arthritis, orchitis, uveitis, iritis, and hepatitis.

Varicella Complications

- Bacterial infection of skin lesions
- Pneumonia
- Central nervous system manifestations
- Reye syndrome (rare)

The risk of complications from varicella varies with age. Complications are infrequent among healthy children. They occur much more frequently in persons older than age 15 years and infants younger than age 1 year. In the prevaccine era, approximately 10,500 persons with varicella required hospitalization each year. Hospitalization rates were approximately 1 to 2 per 1,000 cases among healthy children and 14 per 1,000 cases among adults. The fatality rate for varicella was approximately 1 per 100,000 cases among children age 1 through 14 years, 6 per 100,000 cases among persons age 15 through 19 years, and 21 per 100,000 cases among adults. Most deaths occur in immunocompetent children and adults. Since 1995, when the varicella vaccination program was implemented, hospitalizations and deaths from varicella have declined in the United States 93% and 94%, respectively.

Immunocompromised persons have a high risk of disseminated disease (up to 36% in one report). These persons may have multiple organ system involvement, and the disease may become fulminant and hemorrhagic. The most frequent complications in immunocompromised persons are pneumonia and encephalitis. Children with HIV infection are at increased risk for morbidity from varicella and herpes zoster. Severe and even fatal varicella has been reported in otherwise healthy children on high-dose corticosteroids (e.g., 2 milligrams per kilogram per day or more of prednisone or equivalent) for treatment of asthma and other illnesses.

The onset of maternal varicella from 5 days before to 2 days after delivery may result in overwhelming infection of the neonate, with a fatality ratio as high as 30% if antivirals are not given. This severe disease is the result of fetal exposure to VZV without the benefit of passive maternal antibody. The usual interval from onset of rash in a mother to onset in her neonate is 9 to 15 days but it can be as short as 2 days. Infants born to mothers with onset of maternal varicella more than 5 days prior to delivery usually have a benign course, attributed to passive transfer of maternal antibody across the placenta.

Congenital VZV Infection

- Results from maternal infection in the first 20 weeks of gestation
- Associated with newborn limb hypoplasia, skin scarring, localized muscular atrophy, encephalitis, cortical atrophy, chorioretinitis, microcephaly, and low birth weight

Congenital VZV Infection

Primary maternal varicella infection in the first 20 weeks of gestation is occasionally associated with abnormalities in the newborn, including hypoplasia of an extremity, skin scarring, localized muscular atrophy, encephalitis, cortical atrophy, chorioretinitis, microcephaly, and low birth weight. 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 is very low (less than 2%). Children infected with VZV in utero may develop herpes zoster early in life without having had extrauterine varicella. Isolated case-reports of congenital varicella syndrome have been reported in women infected after 20 weeks of gestation with the latest occurring at 28 weeks of gestation. Rare reports of congenital birth defects following maternal zoster exist, but whether they represent congenital varicella syndrome is unclear.

Laboratory Testing

Laboratory testing, whenever possible, or epidemiological linkage to a typical case or laboratory-confirmed case, should be sought to confirm or rule out varicella. Rapid VZV identification techniques are indicated for a case with severe or unusual disease to initiate specific antiviral therapy. Laboratory techniques in use allow differentiation of wild-type and vaccine strains of VZV.

Polymerase chain reaction (PCR) is the method of choice for laboratory diagnosis of varicella. Real-time PCR methods are

widely available and are the most sensitive and specific of the available tests. Results are available within several hours. If real-time PCR is unavailable, the direct fluorescent antibody (DFA) method can be used, although it is less sensitive than PCR and requires more meticulous specimen collection and handling.

Skin lesions are the preferred sample for laboratory confirmation of varicella. Specimens are best collected by unroofing a vesicle, preferably a fresh fluid-filled vesicle, and then rubbing the base of a skin lesion with a polyester swab. Crusts from lesions are also excellent specimens for PCR. Because viral proteins persist after cessation of viral replication, PCR and DFA may be positive when viral cultures are negative.

PCR testing that discriminates between vaccine and wild-type VZV is available free of charge through the specialized reference laboratories at CDC and the American Public Health Laboratory Association Vaccine Preventable Diseases Reference Centers.

For diagnosis of acute varicella infection, serologic confirmation includes a significant rise in varicella immune globulin class G (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.

A variety of serologic tests for varicella antibody are available commercially to assess disease-induced immunity. Commercial enzyme-linked immunosorbent assays (ELISAs) are recommended for the purpose of screening. There is evidence to suggest that the latex agglutination method, another method to test for serologic IgG, may give false-positive results that could mistakenly categorize a susceptible person as immune.

Antibody resulting from vaccination is generally of lower titer than antibody resulting from varicella disease and commercially available serologic IgG tests are not sufficiently sensitive to detect low levels of antibody following vaccination. Therefore, routine testing for varicella immunity following vaccination is not recommended.

Varicella Epidemiology

- Reservoir
  - Human
- Transmission
  - Person-to-person
  - Direct contact with vesicular fluid or inhalation of aerosols
- Temporal pattern
  - Peak in winter and early spring
- Communicability
  - 1 to 2 days before onset of rash until all lesions have formed crusts

Epidemiology

Occurrence

Varicella occurs worldwide. In countries in temperate climates, it is primarily a childhood disease, with most children infected by age 10 years. In tropical areas, children acquire varicella at older ages and therefore a higher proportion of young adults remain susceptible, resulting in a higher proportion of cases occurring among adults. The reason(s) for this difference in age distribution are not known with certainty.

Reservoir

VZV, the virus that causes both varicella (chickenpox) and zoster (shingles), is an exclusively human pathogen. No animal or insect source or vector is known to exist.

Transmission

VZV transmission occurs person-to-person by direct contact with vesicular fluid or by inhalation of aerosols from vesicular fluid of skin lesions of acute varicella or zoster. Transmission may also occur from infected respiratory tract secretions of patients with varicella that might also be aerosolized. Skin lesions are considered the major source of transmissible VZV. Transmission of VZV would cause varicella, not zoster, in a VZV-naïve person.

Temporal Pattern

In temperate areas, varicella has a distinct seasonal fluctuation, with the highest incidence occurring in winter and early spring. High rates of vaccination coverage in the United States have eliminated discernible seasonality of varicella. Less seasonality is also reported in tropical areas.

Communicability

The period of communicability extends from 1 to 2 days before the onset of rash until all lesions have formed crusts. The virus has not been isolated from crusted lesions. Vaccinated persons who contract varicella may develop lesions that do not crust (macules and papules only). Isolation guidance for these persons is to restrict contact with others until no new lesions appear within a 24-hour period.

Varicella is highly contagious. Secondary attack rates among susceptible household contacts of persons with varicella are between 61% and 100%. Zoster is much less infectious as varicella, i.e., about 1/5 as infectious as varicella.

Varicella Secular Trends in the United States

- Virtually all persons acquired varicella by adulthood before vaccine
- Since vaccine, varicella incidence has declined an average of 97%
  - Decline has occurred in all age groups

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 about 4 million per year. The majority of cases (approximately 90%) occurred among children younger than age 15 years. In the 1990s, the highest age-specific incidence of varicella was among children age 1 to 4 years, 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. Adults age 20 years or older accounted for only 7% of cases.

The incidence of varicella, as well as varicella-related hospitalizations, has decreased significantly since implementation of the national varicella vaccination program in 1995. Overall, varicella incidence declined an average of 97% from prevaccine years (from 1993–1995 to 2013–2014) based on data from four states that have been continuously reporting varicella to the National Notifiable Diseases Surveillance System (NNDSS) since before the varicella vaccination program. Cases declined in all age groups, including infants who are not eligible for vaccination and adults whose rates of vaccination are low, indicating community protection benefits of the vaccination program. The second dose of varicella vaccine was added to the national program in 2007. During the 2-dose era, data from 40 states that reported varicella cases to NNDSS have shown an 85% decline in varicella incidence from 2005–2006 to 2013–2014, with the greatest declines among children age 5 to 14 years (85% to 89%).

One-dose varicella vaccine coverage among children age 19 through 35 months has been 90% to 91% since 2007; varicella vaccination coverage of at least 2 doses among adolescents age 13 through 17 years without a history of varicella has been greater than 85% since 2016.

Varicella Vaccines

Two live, attenuated VZV-containing vaccines for the prevention of varicella are licensed for use in the United States. VAR (Varivax) vaccine is single-antigen varicella vaccine and MMRV (ProQuad) vaccine is a combination measles, mumps, rubella, and varicella vaccine.

Varicella Vaccines

- VAR (Varivax)
- MMRV (ProQuad)

Characteristics

VAR vaccine is derived from the Oka strain of VZV. The virus was attenuated by sequential passage in human embryonic lung cell culture, embryonic guinea pig fibroblasts, and in WI-38 human diploid cells. The Oka/Merck vaccine has undergone further passage through MRC-5 human diploid cell cultures for a total of 31 passages. The vaccine is reconstituted with sterile water and contains gelatin. VAR vaccine is administered by the subcutaneous route. Each dose of VAR vaccine contains neomycin as an antibiotic. It contains no adjuvant or preservative.

Varicella Vaccine Characteristics

- Live, attenuated vaccines
- VAR contains neomycin and gelatin
- MMRV contains neomycin and gelatin
- Administered by subcutaneous injection

MMRV vaccine contains measles, mumps, and rubella virus of equal titer and identical to those in the MMR vaccine. The titer of Oka Varicella-Zoster virus is higher in MMRV vaccine than in VAR, a minimum of 9,772 plaque-forming units (PFU) versus 1,350 PFU, respectively. The vaccine is reconstituted with sterile water and contains gelatin. MMRV vaccine is administered by the subcutaneous route. Each dose of MMRV vaccine contains neomycin as an antibiotic. It contains no adjuvant or preservative.

Varicella Vaccination Schedule

- 2-dose series at age 12 through 15 months and age 4 through 6 years
- Minimum age for dose 1 is 12 months
- Minimum interval for dose 1 to 2 is:
  - 3 months for children age 12 months–12 years (although a 4-week interval is valid)
  - 4 weeks for persons age 13 years and older (VAR only)
- Discuss risks and benefits of MMRV versus separate VAR
  - Separate MMR and VAR vaccines preferred for dose 1 in ages 12 through 47 months
  - MMRV preferred for dose 2 and dose 1 at age 48 months or older

Vaccination Schedule and Use

VAR or MMRV can be used to implement the vaccination recommendations for prevention of varicella. VAR vaccine (Varivax) is licensed for use in persons age 12 months or older. MMRV (ProQuad) is licensed for use in children age 12 months through 12 years.

VAR (Varivax)

VAR vaccine is licensed for use in persons age 12 months or older. It is administered as a 2-dose series. Dose 1 is recommended for children age 12 through 15 months. Dose 2 is recommended at age 4 through 6 years at the same visit as the second dose of MMR vaccine, but may be given as early as 3 months after dose 1 (the minimum interval for children younger than age 13 years). However, if dose 2 is administered at least 4 weeks after dose 1, it does not need to be repeated. For persons age 13 years or older, the minimum interval between doses is 4 weeks. Testing for varicella immunity following 2 doses of vaccine is not necessary because 99% of persons are seropositive after the second dose. Moreover, available commercial assays are not sensitive enough to detect antibody following vaccination in all instances. VAR vaccine has been shown to be safe and effective in healthy children when administered at the same time as MMR vaccine at separate sites and with separate syringes. If varicella and MMR vaccines are not administered at the same visit, they should be separated by at least 4 weeks. Varicella vaccine may be administered simultaneously with all other childhood vaccines.

Children with a clinician-diagnosed or verified history of typical varicella can be assumed to be immune to varicella. Serologic testing of children prior to vaccination is not warranted because the majority of children between age 12 months and 12 years without a clinical history of varicella are not immune. Prior history of varicella is not a contraindication to varicella vaccination, so when in doubt as to history, varicella vaccine should be administered. Because serologic evidence of VZV infection has been documented in 96%-97% of U.S.-born adults age 20-29 years and in 97%-99% of adults age 30 years or older tested during 1998–1999, individuals who were born in the United States before 1980 are considered to have evidence of immunity except for health-care personnel (risk of spreading VZV to high-risk patients), pregnant women (risk of transmission to fetus which might result in congenital varicella syndrome), and immunocompromised persons (risk of severe disease).

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

All health care personnel should be immune to varicella. In health care 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 immunity following vaccination is not necessary. Seroconversion does not always result in full protection against disease, although no data regarding correlates of protection are available for adults. Vaccinated healthcare personnel exposed to VZV should be monitored daily from day 8 to 21 after exposure through the employee health or infection control program to screen for fever, skin lesions, and systemic symptoms. In addition, health care personnel should be instructed to immediately report fever, headache, or other constitutional symptoms and any skin lesions that may be atypical. The person should be placed on sick leave immediately if symptoms occur. The risk of transmission of vaccine virus from a vaccinated person to a susceptible contact is very low, and the benefits of vaccinating susceptible health care personnel clearly outweigh this potential risk.

MMRV (ProQuad)

MMRV vaccine is licensed for use in children age 12 months through 12 years. MMRV vaccine may be used for both dose 1 and dose 2 of measles, mumps, and rubella vaccination and varicella vaccination in children younger than age 13 years. The minimum interval between doses of MMRV is 3 months. However, if dose 2 is administered at least 4 weeks following dose 1, it does not need to be repeated.

For the first dose of measles, mumps, rubella, and varicella vaccines at age 12 through 47 months, either separate MMR and varicella (VAR) vaccines, or MMRV vaccine, may be used. However, the risk of febrile seizures is about twice as high for children receiving MMRV vaccine versus separate MMR and VAR vaccines. Providers who are considering administering MMRV should discuss the benefits and risks of both vaccination options with the parents. Unless the parent or caregiver expresses a preference for MMRV, separate MMR vaccine and VAR vaccine should be administered for the first dose in this age group. For the second dose of measles, mumps, rubella, and varicella vaccines at any age and for the first dose at age 48 months or older, the use of MMRV generally is preferred over separate injections of its equivalent component vaccines (i.e., MMR vaccine and VAR vaccine).

Immunogenicity and Vaccine Efficacy

VAR (Varivax)

After one dose of VAR vaccine, 97% of children age 12 months through 12 years develop detectable antibody titers. More than 90% of vaccine responders maintain antibody for at least 6 years. In Japanese studies, 97% of children had antibody 7 to 10 years after vaccination.

Varicella Vaccine Efficacy

- Effectiveness:
  - 82% for dose 1
  - 92% for dose 2

Among healthy adolescents and adults age 13 years or older, an average of 78% develop antibody after dose 1, and 99% develop antibody after a second dose given 4 to 8 weeks later. Antibody persisted for at least 1 year in 97% of recipients after the second dose.

Immunity appears to be long-lasting, and is probably permanent in the majority of vaccine recipients. Breakthrough infection is significantly milder than infection among unvaccinated persons, with fewer lesions (generally fewer than 50), many of which are maculopapular rather than vesicular. Most persons with breakthrough infection do not have fever. Although findings of some studies have suggested otherwise, most investigations have not identified time since vaccination as a risk factor for breakthrough varicella. Some investigations have identified asthma, use of steroids, and vaccination at younger than age 15 months as risk factors for breakthrough varicella, but other investigations did not.

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

Studies have shown that a second dose of varicella vaccine boosts immunity and reduces the risk of breakthrough disease in children. A meta-analysis of postlicensure estimates found the effectiveness of 1 dose of varicella vaccine to be 82% against any clinical varicella and 98% against severe disease. Two doses of vaccine demonstrated 92% effectiveness against any clinical varicella.

MMRV (ProQuad)

MMRV vaccine was licensed on the basis of non-inferiority of immunogenicity of the antigenic components rather than the clinical efficacy. Clinical studies involving healthy children age 12 through 23 months indicated that those who received a single dose of MMRV vaccine developed similar levels of antibody to measles, mumps, rubella, and varicella as children who received MMR vaccine and VAR vaccine concomitantly at separate injection sites.

Varicella Immunity

- Documentation of age-appropriate vaccination
- Laboratory evidence of immunity
- Laboratory confirmation of disease
- Birth in the U.S. before 1980
  - Exception: Health care personnel, pregnant women, and immunocompromised persons
- Health care provider diagnosis or verification of varicella disease
- History of herpes zoster based on health care provider diagnosis or verification of disease history

Varicella Immunity

Evidence of immunity to varicella includes any of the following:

- Documentation of age-appropriate vaccination:

  - Preschool-aged children (age 12 months or older): 1 dose
  - School-aged children, adolescents, and adults: 2 doses

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

Postexposure Prophylaxis

VAR Vaccine

Data from the United States and Japan in a variety of settings indicate that varicella vaccine is 70% to 100% effective in preventing illness or modifying the severity of illness if used within 3 days, and possibly up to 5 days, after exposure. ACIP recommends the vaccine for postexposure prophylaxis within 3 through 5 days after exposure for persons age 12 months or older who do not have evidence of varicella immunity and who do not have contraindications to vaccination. 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

Varicella Vaccine Postexposure Prophylaxis

- Varicella vaccine is recommended for use in persons age 12 months or older without evidence of varicella immunity within 3 through 5 days after exposure to varicella
  - 70%-100% effective if given within 3 days of exposure (possibly up to 5 days)

increases the risk for vaccine-associated adverse reactions. Although postexposure use of varicella vaccine has potential applications in hospital settings, preexposure vaccination of all health care personnel without evidence of varicella immunity is the recommended and preferred method for preventing varicella in health care settings.

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

Varicella-Zoster Immune Globulin

A Varicella-Zoster Immune Globulin (VZIG [VariZIG]) is licensed for use in the United States for postexposure prophylaxis for persons who do not have evidence of varicella immunity and who have contraindications for varicella vaccine. VariZIG is a purified human immune globulin preparation made from plasma containing high levels of anti-varicella antibodies (IgG) that is lyophilized. When properly reconstituted, VariZIG is approximately a 5% solution of IgG that can be administered intramuscularly.

Patient groups recommended by ACIP to receive VariZIG for postexposure prophylaxis include the following:

- Immunocompromised patients without evidence of immunity to varicella
- Neonates whose mothers have signs and symptoms of varicella around the time of delivery (i.e., 5 days before to 2 days after)
- Hospitalized preterm infants born at 28 weeks gestation or later whose mothers do not have evidence of immunity
- Hospitalized preterm infants born earlier than 28 weeks' gestation or who weigh 1,000 grams or less at birth, regardless of maternal history of varicella disease or vaccination
- Pregnant women without evidence of immunity to varicella

Contraindications and Precautions to Vaccination

As with other vaccines, a history of a severe allergic reaction (anaphylaxis) to a vaccine component or following a prior dose is a contraindication to further doses. Moderate or severe acute illness (with or without fever) in a patient is considered a precaution to vaccination, although persons with minor illness may be vaccinated.

Contraindications and precautions are similar for both varicella-containing vaccines. VAR vaccine and MMRV vaccine both contain minute amounts of neomycin and gelatin but do not contain egg protein. Persons with alpha-gal allergy may wish to consult their physician before receiving a vaccine that contains gelatin.

Persons who are immunosuppressed due to leukemia, lymphoma, generalized malignancy, immune deficiency disease, or immunosuppressive therapy should not be vaccinated with a varicella-containing vaccine. However, treatment with low-dose (e.g., less than 2 milligrams per kilogram of body weight per day), alternate-day, topical, replacement, or aerosolized steroid preparations is not a contraindication to vaccination.

The interval until immune reconstruction varies with the intensity and type of immunosuppressive therapy, radiation therapy, underlying disease, and other factors, complicating the ability to make a definitive recommendation for an interval after cessation of immunosuppressive therapy when live-virus vaccines can be administered safely and effectively. Current recommendations are for patients to be vaccinated with varicella vaccine when in remission and at least three months after cancer chemotherapy, with evidence of restored immunocompetence. Varicella vaccine (as a 2-dose regimen if there is sufficient time) should be administered to immunocompetent patients without evidence of varicella immunity, if it can be administered at least 4 weeks before initiating immunosuppressive therapy.

Other immunosuppressive medications include human immune mediators such as interleukins and colony-stimulating factors, immune modulators, and medicines such as tumor necrosis factor-alpha inhibitors and anti-B cell antibodies. Live vaccines should be withheld 3 months following such therapies, and withheld at least 6 months following therapy with anti-B cell antibodies. Some experts recommend longer than 6 months following anti-B cell antibodies.

A family history of congenital or hereditary immunodeficiency in first-degree relatives (i.e., parents and siblings), unless the immune competence of the potential vaccine recipient has been substantiated clinically or verified by a laboratory, is a contraindication for MMR or MMRV vaccine.

Varicella Vaccine Contraindications

- Contraindication
  - Severe allergic reaction to vaccine component or following a prior dose
  - Immunosuppression due to leukemia, lymphoma, generalized malignancy, immune deficiency disease, or immunosuppressive therapy
  - Family history of congenital or heredity immunodeficiency in first-degree relatives
  - HIV infection*
  - Hematopoietic stem cell transplant (wait 24 months)
  - Pregnancy

*Contraindicated for MMRV; contraindicated for VAR depending on CD4 count

Varicella Vaccine Precautions

- Precaution
  - Moderate or severe acute illness
  - Alpha-gal allergy (consult with physician)
  - Receipt of antibody-containing blood products (wait 3 to 11 months to vaccinate)
  - Need for tuberculosis testing*
  - Receipt of specific antiviral drugs 24 hours before vaccination
  - Simultaneous use of aspirin or aspirin-containing products
  - Personal or family history of seizures of any etiology*

*MMRV only

Persons with severe cellular immunodeficiency resulting from infection with HIV, including persons diagnosed with acquired immunodeficiency syndrome (AIDS) should not receive varicella vaccine. HIV-infected children with CD4+ T-lymphocyte percentage of 15% or higher, and older children and adults with a CD4+ count of 200 per microliter or higher may be considered for vaccination. These persons may receive MMR vaccine and VAR vaccine, but should not receive MMRV vaccine.

The effect of the administration of antibody-containing blood products (e.g., immune globulin, whole blood or packed red blood cells, or intravenous immune globulin) on the response to varicella vaccine virus is unknown. Because of the potential inhibition of the response to vaccination by passively transferred antibodies, neither VAR vaccine nor MMRV vaccine (nor MMR vaccine) should be administered for 3 to 11 months after receipt of antibody-containing blood products. The interval between the antibody-containing blood product and receipt of VAR, MMR, or MMRV vaccine is determined by the type of product administered. Antibody-containing products should not be given for 2 weeks following vaccination unless the benefits exceed those of the vaccine. In such cases, vaccine recipients should either be revaccinated later at the appropriate intervals (ranging 3 to 11 months), or tested for immunity and revaccinated if seronegative.

Varicella-containing vaccines may be administered a minimum of 24 months after hematopoietic stem cell transplant to patients who do not have graft versus host disease, are considered immunocompetent, and whose last dose of intravenous immunoglobulin (IVIG) was 8 to 11 months previously. Nonimmune family members, close contacts, and health care personnel associated with the patient should be vaccinated before that time.

A personal or family (i.e., sibling or parent) history of seizures of any etiology is a precaution for MMRV vaccine. Children with a personal or family history of seizures of any etiology should ideally be vaccinated with separate MMR and VAR vaccines because the risks for using MMRV vaccine in this group of children generally outweigh the benefits.

Receipt of specific antiviral drugs (acyclovir, famciclovir, or valacyclovir) 24 hours before vaccination is a precaution for VAR or MMRV vaccination. These antiviral drugs should be avoided for 14 days after vaccination if possible.

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 testing is not a prerequisite for varicella vaccination.

Simultaneous use of aspirin or aspirin-containing products is a precaution for VAR or MMRV vaccine. The manufacturer recommends that vaccine recipients avoid the use of salicylates for 6 weeks after receiving VAR or MMRV vaccine because of the association between aspirin use and Reye syndrome following varicella.

The need for tuberculin skin testing or interferon-gamma release assay (IGRA) testing is a precaution for MMRV vaccine.

Prior history of varicella is not a contraindication to varicella vaccination, so when in doubt as to history, varicella vaccine should be administered.

Women known to be pregnant or attempting to become pregnant should not receive a varicella-containing vaccine.

Vaccination in Pregnancy

Wild-type varicella poses a low risk to the fetus. Because the virulence of the attenuated virus used in the vaccine is less than that of the wild-type virus, the risk to the fetus, if any, should be even lower from vaccine virus. Because the effects of the varicella virus on the fetus are unknown, pregnant women should not be vaccinated. Nonpregnant women who are vaccinated should avoid becoming pregnant for 1 month after each injection. For persons without evidence of immunity, having a pregnant household member is not a contraindication for vaccination.

Routine pregnancy testing of women of childbearing age before administering a live-virus vaccine is not recommended. If a pregnant woman is inadvertently vaccinated or becomes pregnant within 4 weeks after varicella vaccination, she should be counseled about the theoretical basis of concern for the fetus; however, varicella vaccination during pregnancy should not be considered a reason to terminate pregnancy.

To monitor the pregnancy outcomes of women inadvertently vaccinated with VZV-containing vaccines immediately before or during pregnancy, Merck and CDC established the Merck/CDC Pregnancy Registry for VZV-Containing Vaccines. From inception of the registry in 1995 through March 2012, no cases of congenital varicella syndrome and no increased prevalence of other birth defects have been detected among women vaccinated within 3 months before or during pregnancy. Although a small risk for congenital varicella syndrome cannot be ruled out, the low number of exposures being registered each year in addition to the rarity of the outcome, were too low to improve on the estimate of the risk within a reasonable timeframe. Therefore, new patient enrollment was discontinued as of October 16, 2013. Merck continues to monitor pregnancy outcomes after inadvertent exposures to VZV-containing vaccines during pregnancy or within 3 months

before conception. CDC and the Food and Drug Administration continue to monitor adverse events after vaccination with VZV-containing vaccines through the Vaccine Adverse Event Reporting System (VAERS). New cases of exposure immediately before or during pregnancy or other adverse events after vaccination with VAR vaccine or MMRV vaccine should be reported to Merck (telephone, 1-877-888-4231) and to VAERS (https://vaers.hhs.gov/index.html).

Postpartum vaccination of women without evidence of immunity need not be delayed because of breastfeeding. Single-antigen varicella vaccine should be administered to nursing mothers without evidence of immunity.

Varicella Vaccine Safety

VAR

- Rash at injection site
  - 1–3%
- Generalized rash
  - 4–6%
- Fever
  - 10–15%

MMRV

- Fever of 102ºF or higher
  - 21.5%
- Febrile seizures
  - 1 additional per 2,300 to 2,600 children age 12 through 23 months

Vaccine Safety

The most common adverse reactions following varicella vaccine are local reactions, such as pain, soreness, erythema, and swelling. Based on information from the manufacturer's clinical trials of varicella vaccine, local reactions are reported by 19% of children and by 24% of adolescents and adults (33% following the second dose). These local adverse reactions are generally mild and self-limited. A varicella-like rash at injection site is reported by 3% of children and by 1% of adolescents and adults following the second dose. In both circumstances, a median of two lesions have been present. These lesions generally occur within 2 weeks and may be 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 an average of five lesions. Most of these generalized rashes occur within 3 weeks and may be mainly maculopapular.

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

Varicella vaccine is a live virus vaccine and may result in a latent infection, similar to that caused by wild varicella virus. Consequently, zoster caused by the vaccine virus has been reported. Not all these cases have been confirmed as having been caused by vaccine virus. The risk of zoster following vaccination was assessed among children and is much lower (~79% lower) than that following infection with wild-type virus. The majority of cases of zoster following vaccine have been mild and have not been associated with complications such as postherpetic neuralgia; however, in children cases of herpes zoster with meningitis have been reported.

In MMRV vaccine prelicensure studies conducted among children age 12 to 23 months, fever (reported as abnormal or

elevated greater than or equal to 102°F oral equivalent) was observed 5 to 12 days after vaccination in 21.5% of MMRV vaccine recipients compared with 14.9% of MMR vaccine and VAR vaccine recipients. Measles-like rash was observed in 3.0% of MMRV vaccine recipients compared with 2.1% of those receiving MMR vaccine and VAR vaccine. Two postlicensure studies indicated that one additional febrile seizure per 2,300 to 2,600 children age 12 through 23 months occurred 5 to 12 days after the first dose of MMRV vaccine, compared with children who had received the first dose of MMR vaccine and VAR vaccine administered as separate injections at the same visit. Data from postlicensure studies do not suggest that this increased risk exists for children age 4 to 6 years receiving the second dose of MMRV vaccine.

Transmission of Varicella Vaccine Virus

Accumulated evidence supports that healthy, vaccinated persons have minimal risk for transmitting the varicella vaccine virus to contacts; through 2018 only 13 cases from 11 immunocompetent vaccine recipients have been documented, most commonly among household contacts. Transmission of vaccine virus was reported only from vaccine recipients who developed a varicella-like or herpes zoster rash after vaccination. Secondary cases of varicella caused by the vaccine virus have been typically mild. In studies of household contacts, several instances of asymptomatic seroconversion have been observed. If a vaccinated person develops a rash, it is recommended that close contact with persons who do not have evidence of varicella immunity and who are at high risk of complications of varicella, such as immunocompromised persons, be avoided until the rash has resolved. As a safeguard, medical facilities should consider precautions for personnel in whom rash occurs after vaccination. Health care personnel in whom a vaccine-related rash occurs should avoid contact with persons without evidence of immunity who are at high risk of serious complications until all lesions resolve or no new lesions appear within a 24-hour period.

Vaccine Storage and Handling

For storage and handling specifics, please refer to the manufacturer. For complete information on best practices and recommendations, please refer to CDC's Vaccine Storage and Handling Toolkit, www.cdc.gov/vaccines/hcp/admin/storage/toolkit/storage-handling-toolkit.pdf.

NOTES

Surveillance and Reporting of Varicella

Varicella was removed from the list of nationally notifiable conditions in 1981, but some states continued to report cases to CDC. Varicella was added back to the list of nationally notifiable conditions in 2003. As of 2019, 40 states have been conducting case-based varicella surveillance. For information on guidance for state and local health department staff who are involved in surveillance activities for vaccine-preventable diseases, please consult the Manual for the Surveillance of Vaccine-Preventable Diseases, www.cdc.gov/vaccines/pubs/surv-manual/chapters.html

Acknowledgements

The editors would like to acknowledge Valerie Morelli, Ginger Redmon, Cindy Weinbaum, and Skip Wolfe for their contributions to this chapter.

Selected References

Bialek S, Perella D, Zhang J, et al. Impact of a routine two-dose varicella vaccination program on varicella epidemiology. *Pediatrics* 2013;132(5):e1134-40.

CDC. FDA Approval of an Extended Period for Administering VariZIG for Postexposure Prophylaxis of Varicella. *MMWR* 2012;61(12):212.

CDC. Immunization of health-care personnel. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2011;60(RR-7):1–45.

CDC. Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2007;56(No. RR-4):1–40.

CDC. Updated Recommendations for Use of VariZIG-United States, 2013. *MMWR* 2013;62(28):574–6.

CDC. Use of combination measles, mumps, rubella, and varicella vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2010;59(No. RR-3):1–12.

Galil K, Brown C, Lin F, et al. Hospitalizations for varicella in the United States, 1988 to 1999. *Pediatr Infect Dis* J 2002 Oct;21(10):931–5.

Leung J, Broder K, Marin M. Severe varicella in persons vaccinated with varicella vaccine (breakthrough varicella): a systematic review. *Expert Rev Vaccines* 2017;16(4):391–400.

Leung J, Marin M. Update on trends in varicella mortality during the varicella vaccine era, United States 1990-2016. *Human vaccines & Immunotherapeutics* 2018;14:10, 2460–63.

Lopez A, Zhang J, Marin M. Epidemiology of varicella during the 2-dose varicella vaccination program – United States, 2005-2014. *MMWR* 2016;65:902–5.

Leung J and Harpaz R. Impact of the Maturing Varicella Vaccination Program on Varicella and Related Outcomes in the United States: 1994-2012. *J Pediatric Infect Dis Soc* 2016 Dec;5(4):395–402. doi: 10.1093/jpids/piv044.

Kuter B, Matthews H, Shinefield H, et al. Ten year follow-up of healthy children who received one or two injections of varicella vaccine. *Pediatr Infect Dis J* 2004;23:132–7.

Marin M, Marti M, Kambhampati A, et al. Varicella vaccine effectiveness worldwide: a systematic review and meta-analysis. *Pediatrics* 2016;137:1–10.

NOTES

NOTES

Marin M, Zhang J, Seward J. Near elimination of varicella deaths in the United States following implementation of the childhood vaccination. *Pediatrics* 2011;128:214–20.

Marin M, Leung J, Gershon A. Transmission of vaccine strain varicella-zoster virus: a systematic review. *Pediatrics* 2019;144(3):e20191305

Seward J, Watson B, Peterson C, et al. Varicella disease after introduction of varicella vaccine in the United States, 1995–2000. *JAMA* 2002;287:606–11.

Seward J, Zhang J, Maupin T, et al. Contagiousness of varicella in vaccinated cases: a household contact study. *JAMA* 2004;292:704–8.

Jessica Leung, MPH; Theresa Harrington, MD, MPH&TM; and Kathleen Dooling, MD, MPH

Herpes zoster, also known as zoster, or shingles, is caused by the reactivation of varicella-zoster virus (VZV). The term "herpes zoster" was first used by encyclopedist Celsus in c. 25 BCE to c. 50 AD. Clinical observations of the relationship between varicella and herpes zoster were made in 1888 by James von Bokay, when children who never had varicella (chickenpox) developed varicella after contact with a person with herpes zoster (shingles). In 1954, Thomas Weller used cell culture to isolate VZV from vesicular fluid of patients with varicella or zoster. However, it was not until 1965 that Edgar Hope-Simpson hypothesized that herpes zoster was due to the reactivation of latent VZV. The first vaccine to reduce the risk of herpes zoster was licensed in the United States in 2006.

Herpes Zoster

- Caused by reactivation of varicella-zoster virus (VZV)
- Observed relationship between varicella and herpes zoster in 1888
- Hypothesis formed in 1965 that herpes zoster was due to reactivation of latent VZV
- First vaccine to reduce risk of herpes zoster licensed in the U.S. in 2006

Varicella-Zoster Virus (VZV)

VZV is a DNA virus and is a member of the herpesvirus family. Like other herpesviruses, VZV persists in the body as a latent infection after the primary (first) infection; VZV persists in sensory nerve ganglia. Primary infection with VZV results in varicella (chickenpox). Latent infection can reactivate resulting in herpes zoster (or shingles).

The virus has a short survival time in the environment.

Varicella-Zoster Virus (VZV)

- DNA virus
- Member of herpesvirus family
- Persists as latent infection

Pathogenesis

Herpes zoster is the result of reactivation of latent VZV infection. During the primary (first) infection (i.e. varicella), VZV travels to the sensory ganglia where it resides permanently. In this latent form, replication is suppressed by the host immune system and VZV is noninfectious but can reactivate to form intact virions in the involved sensory neurons. Reactivated virions travel to epithelial cells resulting in a rash within the dermatome innervated by the sensory nerve. The immunologic mechanism that controls latency of VZV is not well understood. However, factors associated with increased risk of developing herpes zoster disease include aging, immunosuppression, intrauterine exposure to VZV, and having had varicella at younger than age 18 months.

Zoster Pathogenesis

- Result of reactivation of latent VZV infection
- Immunologic mechanism for VZV latency not well understood
- Risk factors: Aging, immunosuppression, intrauterine exposure to VZV, history of varicella at younger than age 18 months

Clinical Features

A vesicular eruption of zoster generally occurs unilaterally in the distribution of a sensory nerve or dermatome and does not cross the mid-line. Zoster can occur in any dermatome but occurs most often in the trunk or face. Two to four days prior to the eruption, there may be pain and paresthesia in the involved area. Zoster rash are initially red macules and papules but progresses to form clusters of vesicular lesions before crusting over. The rash lasts for 7–10 days with healing in 2–4 weeks.

Zoster Clinical Features

- Variable and usually less severe in children and younger adults
- Vesicular eruption occurring most often in the trunk or face
- Rash lasts for 7–10 days with healing in 2–4 weeks
- Immunocompromised persons experience more systemic symptoms

In healthy persons there are few systemic symptoms. In immunocompromised persons, zoster may disseminate, causing generalized skin lesions and central nervous system, pulmonary, and hepatic involvement.

Zoster Complications

- Postherpetic neuralgia (PHN) most common
- Ophthalmic involvement, bacterial superinfection, cranial and peripheral nerve palsies, and visceral involvement

Complications

The most common and debilitating complication from zoster is postherpetic neuralgia (PHN). PHN is pain that persists in the area of the initial rash occurrence after the lesions have resolved. Treatment of persons with PHN is complex, with varying degrees of success in controlling the chronic pain. PHN can last for weeks or months and occasionally may last a year or longer after the resolution of the rash. In addition to PHN, other complications from zoster include ophthalmic involvement, bacterial superinfection, cranial and peripheral nerve palsies, and visceral involvement, all of which often result in severe sequelae.

Laboratory Testing

The diagnosis of zoster is usually made clinically. In some cases where disease is atypical, such as in persons with altered immunocompetence, laboratory testing can be performed, although a positive result does not differentiate zoster from varicella. Polymerase chain reaction (PCR) to detect VZV DNA is the most useful test for confirming cases of zoster. The ideal samples for PCR testing are swabs of unroofed vesicular lesions and scabs from crusted lesions. Direct fluorescent antibody (DFA) and Tzanck smear are not recommended due to limited sensitivity. Serologic methods have limited use for laboratory confirmation of herpes zoster. Although not widely available, there is a serologic test, VZV IgG avidity test, which may be used to distinguish primary infection from reactivation or reinfection.

Zoster Epidemiology

- Reservoir
  - Human
- Transmission
  - Person-to-person
  - Direct contact with vesicular fluid or inhalation of aerosols
- Temporal pattern
  - No temporal pattern
- Communicability
  - From rash onset until lesions crust
  - 1/5 as infectious as varicella

Epidemiology

Occurrence

Zoster occurs worldwide. In the United States, about 1 in 3 people will develop zoster in their lifetime. Although zoster can occur at any age, the incidence increases with advancing age due to waning immunity. Approximately 50% of persons who live to age 85 years will have experienced zoster.

Reservoir

VZV, which is the same virus that causes both varicella and zoster, is an exclusively human pathogen. No animal or insect source or vector is known to exist.

Transmission

VZV transmission occurs person-to-person by direct contact with vesicular fluid or inhalation of aerosols from vesicular fluid of skin lesions of persons with acute varicella or zoster.

Transmission may also occur from infected respiratory tract secretions of patients with varicella that might also be aerosolized. Skin lesions are considered the major source of transmissible VZV. Transmission of VZV would cause varicella, not zoster, in a VZV-naïve person.

Temporal Pattern

Zoster has no seasonal variation and occurs throughout the year.

Communicability

A person with localized zoster is contagious beginning from rash onset until their lesions crust. Persons are less likely to transmit if their lesions are completely covered. Zoster is about 1/5 as infectious as varicella.

Secular Trends in the United States

An estimated 1 million episodes of zoster occur annually in the United States. The lifetime risk of zoster is estimated to be at least 32%. Increasing age and cellular immunosuppression are the most important risk factors; 50% of persons living until age 85 years will develop zoster. Rates of zoster are decreasing in the United States in children younger than age 18 years and in older adults.

Among adults age 60 years or older in 2017, 34.9% had ever received a herpes zoster vaccine.

Zoster Secular Trends in the United States

- Estimated 1 million zoster episodes occur annually in U.S.
- Lifetime risk 32%
- Increasing age and cellular immunosuppression most important risk factors

Zoster Vaccines

RZV (Shingrix) vaccine is a recombinant subunit vaccine and is currently the only zoster vaccine licensed and available for use in the United States. ZVL (Zostavax) vaccine, a live, attenuated zoster vaccine, was also available for use in the United States from 2006 until 2020, when its production for U.S. distribution was discontinued.

Zoster Vaccines

- RZV (Shingrix)

Characteristics

RZV vaccine contains recombinant glycoprotein E in combination with a novel adjuvant ($AS01_B$). The lyophilized antigen component is reconstituted with the adjuvant suspension component. RZV vaccine is administered by intramuscular injection. Each dose of RZV vaccine contains DOPC and $ASO1_B$ as adjuvants. It contains no antibiotic or preservative.

Zoster Vaccine Characteristics

- Contains novel adjuvant
- Administered by intramuscular injection

Zoster Vaccination Schedule

- 2-dose series at 0, 2–6 months in persons age 50 years or older

Vaccination Schedule and Use

RZV vaccine is licensed for use in persons age 50 years or older. RZV vaccine is recommended for immunocompetent adults age 50 years or older, including those who have previously received ZVL or varicella vaccine. Persons with a previous history of shingles may also be vaccinated. Adults 50 years or older do not need to be screened for history of varicella infection prior to vaccination. RZV vaccine is administered as 2-dose series. Dose 2 is administered between 2 and 6 months after dose 1. If more than 6 months have elapsed between doses, the RZV vaccine series does not need to be restarted. However, a second dose given less than 4 weeks after the first dose should be repeated.

Zoster Vaccine Use

- Immunocompetent persons age 50 years or older indicated for vaccination, including:
  - Persons who have previously received ZVL or varicella vaccine
  - Persons with a previous history of shingles

Because estimates of efficacy against both herpes zoster and PHN are higher for RZV than for ZVL, and because ZVL efficacy wanes substantially during the 4 years following receipt when compared to RZV, the Advisory Committee on Immunization Practices (ACIP) issued a preferential recommendation for RZV over ZVL in 2017, when both vaccines were in use.

Persons who have received ZVL vaccine should be revaccinated with a 2-dose series of RZV vaccine. Intervals shorter than 5 years between administration of ZVL vaccine and RZV vaccine have not been studied; however there are no data or theoretical concerns suggesting that RZV vaccine administered sooner than 5 years after ZVL would be less safe or effective. Because ZVL vaccine has been shown to be less efficacious when administered at age 70 years or older, providers might consider the age at which ZVL vaccine was administered when considering the interval between the two vaccines. Based on expert opinion, RZV vaccine should not be given less than 2 months after receipt of ZVL vaccine.

RZV vaccine may be administered concomitantly (at different anatomic sites) with other adult vaccines, including PPSV23 (Pneumovax 23) and annual seasonal influenza vaccine. Evaluation of coadministration with most other adult vaccines is ongoing, but there is currently no evidence of efficacy or safety concerns.

Zoster Vaccine Efficacy

- Phase III multicenter clinical trial efficacy:
  - 96.6% for participants age 50 through 59 years
  - 97.4% for participants age 60 through 69 years
  - 91.3% for participants age 70 years or older

Immunogenicity and Vaccine Efficacy

Efficacy of RZV was evaluated in a two-part, phase III multicenter clinical trial enrolling more than 30,000 participants. Efficacy for prevention of herpes zoster after more than 3 years was 96.6% for participants age 50 through 59 years, 97.4% for participants age 60 through 69 years, and 91.3% for participants age 70 years or older. Efficacy for prevention of PHN was 91.2% for participants age 50 years or older and 88.8% for participants age 70 years or older in a pooled analysis.

Postexposure Prophylaxis

Exposure to a person with either varicella or herpes zoster does not cause zoster in the exposed susceptible person, but rather varicella. Zoster vaccine has no role in the postexposure management of varicella or zoster and should not be used for that purpose. Persons without evidence of immunity who are exposed to varicella or herpes zoster are recommended to receive varicella vaccine within 3 days, and possibly up to 5 days, after exposure. For persons exposed to varicella or herpes zoster who cannot receive varicella vaccine, varicella-zoster immune globulin (VariZIG) can prevent varicella from developing or lessen the severity of the disease.

Varicella Immunity

Evidence of immunity to varicella includes any of the following:

- Documentation of age-appropriate vaccination:
  - Preschool-aged children (age 12 months or older): 1 dose
  - School-aged children, adolescents, and adults: 2 doses
- Laboratory evidence of immunity: commercial assays can be used to assess disease-induced immunity, but they lack adequate sensitivity to reliably detect vaccine-induced immunity (i.e., they may yield false negative results).
- Laboratory confirmation of disease.
- Birth in the United States before 1980 (except for health care personnel, pregnant women, and immunocompromised persons for whom birth in the United States before 1980 should not be considered evidence of immunity). Persons born outside the United States should meet one of the other criteria for varicella immunity.
- A health care provider diagnosis or verification of varicella disease: verification of history or diagnosis of typical disease can be done by any healthcare provider (e.g., school or occupational clinic nurse, nurse practitioner, physician assistant, physician). For persons reporting a history of or presenting with atypical and/or mild cases, assessment by a physician or designee is recommended, and one of the following should be sought: a) an epidemiologic link to a typical varicella case, or b) evidence of laboratory confirmation if laboratory testing was performed at the time of acute disease. When such documentation is lacking, a person should not be considered as having a valid history of disease, because other diseases may mimic mild or atypical varicella.
- History of herpes zoster based on health care provider diagnosis or verification of disease history.

Zoster Vaccine Contraindications and Precautions

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

Contraindications and Precautions to Vaccination

As with other vaccines, a history of a severe allergic reaction (anaphylaxis) to a vaccine component or following a prior dose is a contraindication to further doses. Moderate or severe acute illness (with or without fever) in a patient is considered a precaution to vaccination, although persons with minor illness may be vaccinated.

Persons with chronic medical conditions should receive RZV vaccine unless a contraindication or precaution exists.

Although RZV vaccine is approved for all persons age 50 years or older, immunocompromised persons, including those on moderate- to high- doses of immunosuppressive therapy, were excluded from efficacy studies. Therefore, ACIP has not yet made recommendations regarding use of RZV vaccine in those persons. However, ACIP recommends RZV vaccine for persons taking low-dose immunosuppressive therapy (e.g., less than 20 mg/day of prednisone or equivalent, or using inhaled or topical steroids), or who are anticipating immunosuppression or have recovered from an immunocompromising illness.

Adults age 50 years or older with a history of herpes zoster should receive RZV vaccine. If a patient is experiencing an acute episode of herpes zoster, vaccination should be delayed until the acute stage of the illness has resolved and symptoms abate.

Vaccination in Pregnancy

There are no available data to establish whether RZV vaccine is safe in pregnant or lactating women, and there is currently no ACIP recommendation for use of RZV vaccine in these populations. Consider delaying vaccination until after delivery and lactation.

Zoster Vaccine Safety

- Injection site pain
  - 78%
- Myalgia
  - 45%
- Fatigue
  - 45%

Vaccine Safety

The most common solicited adverse reactions from two placebo-controlled clinical studies involving 29,305 subjects were injection-site pain (78%), myalgia (45%), and fatigue (45%). Serious adverse events were examined in eight studies; overall, rates of serious adverse events were similar in vaccine and placebo groups. Injection-site and systemic grade 3 (i.e., side effects that are severe or medically significant but not immediately life-threatening) solicited adverse events were surveyed in eight studies. Among 9,963 subjects, 16.5% of vaccine recipients, compared with 3.1% of placebo recipients, reported any grade 3 adverse event. Grade 3 injection-site reactions (pain, redness, and swelling) were reported by 9.4% of vaccine recipients and 0.3% of placebo recipients.

Grade 3 solicited systemic events (myalgia, fatigue, headache, shivering, fever, and gastrointestinal symptoms) were reported by 10.8% of vaccine recipients and 2.4% of placebo recipients. Grade 3 local reactions were reported with equal frequency following doses 1 and 2, but Grade 3 systemic reactions were reported more frequently after dose 2. Data informing whether a person will experience a more severe reaction after the second dose, if they had a moderate or severe reaction after the first dose, are lacking.

Before vaccination, providers should counsel recipients about expected systemic and local reactogenicity. Recipients should be encouraged to complete the series even if they experienced a grade 1 to 3 reaction after the first dose.

RZV vaccine does not cause varicella as it is a recombinant vaccine and does not contain live virus.

In a postmarketing observational study, an increased risk of Guillain-Barré syndrome (GBS) was observed during the 42 days following vaccination with Shingrix in adults 65 years of age and older. Based on this evaluation, FDA has determined that there is an association of GBS with Shingrix, but that available evidence is insufficient to establish a causal relationship. FDA has concluded that revision to the Warnings and Precautions section of the Prescribing Information for Shingrix to include a warning about GBS is warranted. FDA has determined that the benefits of vaccination with Shingrix continue to outweigh its risks.

The vaccination recommendations for Shingrix remain the same. CDC and collaborators will continue safety monitoring of Shingrix in the Vaccine Adverse Event Reporting System (VAERS) and the Vaccine Safety Datalink (VSD).

Vaccine Storage and Handling

Before reconstitution, both lyophilized antigen component vials and adjuvant suspension component vials should be stored refrigerated between 2°C and 8°C (36°F and 46°F) and protected from light. After reconstitution, use immediately or store refrigerated between 2°C and 8°C (36°F and 46°F). Discard if not used within 6 hours of reconstitution or if frozen. Manufacturer package inserts contain additional information. For complete information on best practices and recommendations, please refer to CDC's *Vaccine Storage and Handling Toolkit*, www.cdc.gov/vaccines/hcp/admin/storage/toolkit/storage-handling-toolkit.pdf.

NOTES

Surveillance and Reporting of Zoster

Zoster is not a nationally notifiable condition in the United States. For information on guidance for state and local health department staff who are involved in surveillance activities for vaccine-preventable diseases, please consult the Manual for the Surveillance of Vaccine-Preventable Diseases, www.cdc.gov/vaccines/pubs/surv-manual/chapters.html .

Acknowledgements

The editors would like to acknowledge Jennifer Hamborsky, Valerie Morelli, Ginger Redmon, Cindy Weinbaum, and Skip Wolfe for their contributions to this chapter.

Selected References

CDC. Immunization of health-care personnel. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2011;60(RR-7):1–45.

CDC. Prevention of herpes zoster. Recommendations of the Advisory Committee on Immunization Practices. *MMWR* 2008;57(No.RR-5).

CDC. Recommendations of the Advisory Committee on Immunization Practices for Use of Herpes Zoster Vaccines. *MMWR* 2018;67(No. 3):103–8.

CDC. Update on Recommendations for use of Herpes Zoster Vaccine. *MMWR* 2014;66(33):729–31.

Cunningham A, Lal H, Kovac M, et al. Efficacy of the herpes zoster subunit vaccine in adults 70 years of age or older. *NEJM* 2016;375(11):1019–32.

Galetta K, Gilden D. Zeroing in on zoster: A tale of many disorders produced by one virus. *J Neurol Sci* 2015;358(1-2):38–45.

Grading of Recommendations, Assessment, Development, and Evaluation (GRADE): Recombinant Zoster Vaccine (RZV) and Herpes Zoster Live-Attenuated Vaccine (ZVL). www.cdc.gov/vaccines/acip/recs/grade/herpes-zoster.html, accessed August 28, 2020.

Harpaz R, Leung J. The Epidemiology of Herpes Zoster in the United States During the Era of Varicella and Herpes Zoster Vaccines: Changing Patterns Among Children. *Clin Infect Dis* 2019;69(2):345–7.

Harpaz R, Leung J. The Epidemiology of Herpes Zoster in the United States During the Era of Varicella and Herpes Zoster Vaccines: Changing Patterns Among Older Adults. *Clin Infect Dis* 2019;69(2):341–4.

Hesse E, Shimabukuro T, Su J, et al. Postlicensure Safety Surveillance of Recombinant Zoster Vaccine (Shingrix) - United States, October 2017-June 2018. *MMWR* 2019 Feb 1;68(4):91–4.

Lal H, Cunningham A, Godeaux O, et al. Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. *NEJM* 2015;372(22):2087–96.

Nagel M, Bubak A. Varicella Zoster Virus Vasculopathy. *J Infect Dis* 2018;218(Suppl_2):s107–12.

NOTES

NOTES

Oxman M, Levin M, Johnson G, et.al. A Vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *NEJM* 2005; 352(12): 2271–84.

Schmader K, Levin M, Gnann J, et al. Efficacy, safety, and tolerability of herpes zoster vaccine in persons aged 50-59 years. *Clin Inf Dis* 2012;54(7):922–8.

Tseng H, Bruxvoort K, Ackerson B, et al. The epidemiology of herpes zoster in immunocompetent, unvaccinated adults ≥50 years old: incidence, complications, hospitalization, mortality, and recurrence. *J Infect Dis*. 2019;222(5):798–806.

U.S. Food and Drug Administration. FDA requires a warning about Guillain-Barre Syndrome (GBS) be included in the prescribing information for Shingrix. https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/fda-requires-warning-about-guillain-barre-syndrome-gbs-be-included-prescribing-information-shingrix. Accessed April 9, 2021.

Zhang Y, Luo G, Huang Y, et al. Risk of Stroke/Transient Ischemic Attack or Myocardial Infarction with Herpes Zoster: A Systematic Review and Meta-Analysis. *J Stroke Cerebrovasc Dis* 2017;26(8):1807–16.

Appendix A: Schedule and Recommendations

Catch-up Schedule Job Aids for Persons Aged 0 Through 18 Years:

Appendix A

Catch-Up Guidance for Children 4 Months through 6 Years of Age

Diphtheria-, Tetanus-, and Pertussis-Containing Vaccines: DTaP/DT[1]

The table below provides guidance for children whose vaccinations have been delayed. Start with the child's age and information on previous doses (previous doses must be documented and must meet minimum age requirements and minimum intervals between doses). Use this table in conjunction with table 2 of the Recommended Child and Adolescent Immunization Schedule for Ages 18 Years or Younger, found at www.cdc.gov/vaccines/schedules/hcp/child-adolescent.html.

IF current age is	AND # of previous doses of DTaP or DT is	AND	THEN	Next dose due
4 months through 11 months	Unknown or 0	→	Give Dose 1 (DTaP) today	Give Dose 2 (DTaP) at least 4 weeks after Dose 1
	1	It has been at least 4 weeks since Dose 1	Give Dose 2 (DTaP) today	Give Dose 3 (DTaP) at least 4 weeks after Dose 2
		It has **not** been at least 4 weeks since Dose 1	No dose today	Give Dose 2 (DTaP) at least 4 weeks after Dose 1
	2	It has been at least 4 weeks since Dose 2	Give Dose 3 (DTaP) today	Give Dose 4 (DTaP) at least 6 calendar months after Dose 3 **and** at 15 months of age or older[2]
		It has **not** been at least 4 weeks since Dose 2	No dose today	Give Dose 3 (DTaP) at least 4 weeks after Dose 2
1 through 3 years	Unknown or 0	→	Give Dose 1 (DTaP) today	Give Dose 2 (DTaP) at least 4 weeks after Dose 1
	1	It has been at least 4 weeks since Dose 1	Give Dose 2 (DTaP) today	Give Dose 3 (DTaP) at least 4 weeks after Dose 2
		It has **not** been 4 weeks since Dose 1	No dose today	Give Dose 2 (DTaP) at least 4 weeks after Dose 1
	2	It has been at least 4 weeks since Dose 2	Give Dose 3 (DTaP) today	Give Dose 4 (DTaP) at least 6 calendar months after Dose 3
		It has **not** been 4 weeks since Dose 2	No dose today	Give Dose 3 (DTaP) at least 4 weeks after Dose 2
	3	It has been at least 6 calendar months since Dose 3	If 12 through 14 months of age, no dose today[2]	Give Dose 4 (DTaP) at 15 through 18 months of age
			If 15 months of age or older, give Dose 4 (DTaP) today	Give Dose 5 (DTaP) at least 6 months after Dose 4 **and** at 4 through 6 years of age
		It has **not** been 6 calendar months since Dose 3	No dose today	Give Dose 4 (DTaP) at least 6 months after Dose 3

[1]Vaccine information: DTaP–Administer to children 6 weeks through 6 years of age without a contraindication or precaution to diphtheria, tetanus, or pertussis vaccine. DTaP products include Daptacel, Kinrix, Infanrix, Pediarix, Pentacel, and Quadracel. Use the correct product based on the approved age indications. DT–Administer to children 6 weeks through 6 years of age with a contraindication to pertussis vaccine.

[2]The fourth dose may be administered as early as age 12 months, provided at least 6 months have elapsed since the third dose.

Reference: Recommended Child and Adolescent Immunization Schedule for Ages 18 Years or Younger—United States, 2021. www.cdc.gov/vaccines/schedules/downloads/child/0-18yrs-child-combined-schedule.pdf

Revised February 2021

Catch-Up Guidance for Children 4 Months through 6 Years of Age

Diphtheria-, Tetanus-, and Pertussis-Containing Vaccines: DTaP/DT[1]

IF current age is	AND # of previous doses of DTaP or DT is[1]	AND	AND	THEN	Next dose due
4 through 6 years	Unknown or 0	→	→	Give Dose 1 (DTaP) today	Give Dose 2 (DTaP) at least 4 weeks after Dose 1
	1	It has been at least 4 weeks since Dose 1	→	Give Dose 2 (DTaP) today	Give Dose 3 (DTaP) at least 4 weeks after Dose 2
		It has **not** been 4 weeks since Dose 1	→	No dose today	Give Dose 2 (DTaP) at least 4 weeks after Dose 1
	2	It has been at least 4 weeks since Dose 2	→	Give Dose 3 (DTaP) today	Give Dose 4 (DTaP) at least 6 calendar months after Dose 3
		It has **not** been at least 4 weeks since Dose 2	→	No dose today	Give Dose 3 (DTaP) at least 4 weeks after Dose 2
	3	It has been at least 6 calendar months since Dose 3	→	Give Dose 4 (DTaP) today	Give Tdap at 11 to 12 years of age
		It has **not** been at least 6 calendar months since Dose 3	→	No dose today	Give Dose 4 (DTaP) at least 6 calendar months after Dose 3
	4	All doses were given prior to the 4th birthday	It has not been at least 6 months since Dose 4	No dose today	Give Dose 5 (DTaP) at least 6 calendar months after Dose 4
			It has been at least 6 months since Dose 4	Give Dose 5 (DTaP) today	Give Tdap at 11 to 12 years of age
		At least one dose was given at/after the 4th birthday	→	No dose today	

[1]Vaccine information: DTaP–Administer to children 6 weeks through 6 years of age without a contraindication or precaution to diphtheria, tetanus, or pertussis vaccine. DTaP products include Daptacel, Kinrix, Infanrix, Pediarix, Pentacel, and Quadracel. Use the correct product based on the approved age indications. DT–Administer to children 6 weeks through 6 years of age with a contraindication to pertussis vaccine.

Reference: Recommended Child and Adolescent Immunization Schedule for Ages 18 Years or Younger—United States, 2021.
www.cdc.gov/vaccines/schedules/downloads/child/0-18yrs-child-combined-schedule.pdf

Catch-Up Guidance for Healthy[1] Children 4 Months through 4 Years of Age

Haemophilus influenzae type B Vaccines: ActHIB, Pentacel, Hiberix, or Unknown

The table below provides guidance for children whose vaccinations have been delayed. Start with the child's age and information on previous doses (previous doses must be documented and must meet minimum age requirements and minimum intervals between doses). Use this table in conjunction with table 2 of the Recommended Child and Adolescent Immunization Schedule for Ages 18 Years or Younger, found at www.cdc.gov/vaccines/schedules/hcp/child-adolescent.html.

IF current age is	AND # of previous doses is	AND		THEN	Next dose due
4 through 6 months	Unknown or 0	→		Give Dose 1 today	Give Dose 2 at least 4 weeks after Dose 1
	1	It has been at least 4 weeks since Dose 1		Give Dose 2 today	Give Dose 3 at least 4 weeks after Dose 2
		It has **not** been 4 weeks since Dose 1		No dose today	Give Dose 2 at least 4 weeks after Dose 1
	2	It has been at least 4 weeks since Dose 2		Give Dose 3 today	Give Dose 4 (**Final Dose**) at 12 months of age or older
		It has **not** been 4 weeks since Dose 2		No dose today	Give Dose 3 at least 4 weeks after Dose 2
7 through 11 months	Unknown or 0	→	→	Give Dose 1 today	Give Dose 2 at least 4 weeks after Dose 1
	1	It has been at least 4 weeks since Dose 1	→	Give Dose 2 today	IF Dose 1 was given **before** 7 months of age, give Dose 3 at least 4 weeks after Dose 2
					IF Dose 1 was given at 7 months of age or older, give Dose 3 (**Final Dose**) at least 8 weeks after Dose 2 **and** no earlier than 12 months of age
		It has **not** been 4 weeks since Dose 1	→	No dose today	Give Dose 2 at least 4 weeks after Dose 1
	2	Dose 1 was given **before** 7 months of age	It has been at least 4 weeks since Dose 2	Give Dose 3 today	Give Dose 4 (**Final Dose**) at least 8 weeks after Dose 3 **and** no earlier than 12 months of age
			It has **not** been 4 weeks since Dose 2	No dose today	Give Dose 3 at least 4 weeks after Dose 2
		Dose 1 was given at 7 months of age or older	→	No dose today	Give Dose 3 (**Final Dose**) at least 8 weeks after Dose 2 **and** no earlier than 12 months of age

[1] Refer to notes of the Recommended Child and Adolescent Immunization Schedule for Ages 18 Years or Younger–United States, 2021, for immunization guidance for children at increased risk for Haemophilus influenzae type b disease.

Reference: Recommended Child and Adolescent Immunization Schedule for Ages 18 Years or Younger–United States, 2021. www.cdc.gov/vaccines/schedules/downloads/child/0-18yrs-child-combined-schedule.pdf

Catch-Up Guidance for Healthy[1] Children 4 Months through 4 Years of Age

Haemophilus influenzae type B Vaccines: ActHIB, Pentacel, Hiberix, or Unknown

IF current age is	AND # of previous doses is	AND	AND	AND	THEN	Next dose due
12 through 14 months	Unknown or 0	→	→	→	Give Dose 1 today	Give Dose 2 (**Final Dose**) at least 8 weeks after Dose 1
	1	Dose 1 was given **before** 12 months of age	It has been at least 4 weeks since Dose 1	→	Give Dose 2 today	Give Dose 3 (**Final Dose**) at least 8 weeks after Dose 2
			It has **not** been 4 weeks since Dose 1	→	No dose today	Give Dose 2 at least 4 weeks after Dose 1
		Dose 1 was given at 12 months of age or older	It has been at least 8 weeks since Dose 1	→	Give Dose 2 (**Final Dose**) today	**No additional doses needed**
			It has **not** been 8 weeks since Dose 1	→	No dose today	Give Dose 2 (**Final Dose**) at least 8 weeks after Dose 1
	2	Dose 1 was given **before** 12 months of age	It has been at least 8 weeks since Dose 2	→	Give Dose 3 (**Final Dose**) today	**No additional doses needed**
			It has **not** been 8 weeks since Dose 2	→	No dose today	Give Dose 3 (**Final Dose**) at least 8 weeks after Dose 2
		Dose 1 was given at 12 months of age or older	→	→	No dose today	**No additional doses needed**
	3	All doses were given **before** 12 months of age	→	It has been at least 8 weeks since Dose 3	Give Dose 4 (**Final Dose**) today	**No additional doses needed**
				It has **not** been 8 weeks since Dose 3	No dose today	Give Dose 4 (**Final Dose**) at least 8 weeks after Dose 3
		At least one dose was given at 12 months of age or older	→	→	No dose today	**No additional doses needed**

[1] Refer to notes of the Recommended Child and Adolescent Immunization Schedule for Ages 18 Years or Younger–United States, 2021, for children at increased risk for *Haemophilus influenzae* type b disease.

Reference: Recommended Child and Adolescent Immunization Schedule for Ages 18 Years or Younger–United States, 2021. www.cdc.gov/vaccines/schedules/downloads/child/0-18yrs-child-combined-schedule.pdf

Catch-Up Guidance for Healthy[1] Children 4 Months through 4 Years of Age

Haemophilus influenzae type B Vaccines: ActHIB, Pentacel, Hiberix, or Unknown

IF current age is	AND # of previous doses is	AND	AND	AND	THEN	Next dose due
15 through 59 months	Unknown or 0	→	→	→	Give Dose 1 (**Final Dose**) today	**No additional doses needed**
	1	Dose 1 was given **before** 12 months of age	→	→	Give Dose 2 (**Final Dose**) today	**No additional doses needed**
		Dose 1 was given at 12 through 14 months of age	It has been at least 8 weeks since Dose 1	→	Give Dose 2 (**Final Dose**) today	**No additional doses needed**
			It has **not** been 8 weeks since Dose 1	→	No dose today	Give Dose 2 (**Final Dose**) at least 8 weeks after Dose 1
		Dose 1 was given at 15 months of age or older	→	→	No dose today	**No additional doses needed**
	2	Dose 1 was given **before** 12 months of age	Dose 2 was given **before** 15 months of age	It has been at least 8 weeks since Dose 2	Give Dose 3 (**Final Dose**) today	**No additional doses needed**
				It has **not** been 8 weeks since Dose 2	No dose today	Give Dose 3 (**Final Dose**) at least 8 weeks after Dose 2
			Dose 2 was given at 15 months of age or older	→	No dose today	**No additional doses needed**
		Dose 1 was given at 12 months of age or older	→	→	No dose today	**No additional doses needed**
	3	Dose 3 was given **before** 15 months of age	All doses were given **before** 12 months of age	→	Give Dose 4 (**Final Dose**) today	**No additional doses needed**
			At least one dose was given at 12 months of age or older	→	No dose today	**No additional doses needed**
		Dose 3 was given at 15 months of age or older	→	→	No dose today	**No additional doses needed**

[1] Refer to notes of the Recommended Child and Adolescent Immunization Schedule for Ages 18 Years or Younger–United States, 2021, for immunization guidance for children at increased risk for Haemophilus influenzae type b disease.

Reference: Recommended Child and Adolescent Immunization Schedule for Ages 18 Years or Younger–United States, 2021. www.cdc.gov/vaccines/schedules/downloads/child/0-18yrs-child-combined-schedule.pdf

Catch-Up Guidance for Healthy[1] Children 4 Months through 4 Years of Age

Haemophilus influenzae type b Vaccines: PedvaxHIB Vaccine Only

The table below provides guidance for children whose vaccinations have been delayed. Start with the child's age and information on previous doses (previous doses must be documented and must meet minimum age requirements and minimum intervals between doses). Use this table in conjunction with table 2 of the Recommended Child and Adolescent Immunization Schedule for Ages 18 Years or Younger, found at www.cdc.gov/vaccines/schedules/hcp/child-adolescent.html.

IF current age is	AND # of previous doses is	AND	AND	THEN	Next dose due
4 through 6 months	0	→	→	Give Dose 1 today	Give Dose 2 at least 4 weeks after Dose 1
	1	→	It has been at least 4 weeks since Dose 1	Give Dose 2 today	Give Dose 3 (**Final Dose**) at 12 months of age or older
		→	It has **not** been 4 weeks since Dose 1	No dose today	Give Dose 2 at least 4 weeks after Dose 1
7 through 11 months	0	→	→	Give Dose 1 today	Give Dose 2 at least 4 weeks after Dose 1
	1	→	It has been at least 4 weeks since Dose 1	Give Dose 2 today	Give Dose 3 (**Final Dose**) at least 8 weeks after Dose 2 **and** at 12 months of age or older
		→	It has **not** been 4 weeks since Dose 1	No dose today	Give Dose 2 at least 4 weeks after Dose 1
12 through 14 months	0	→	→	Give Dose 1 today	Give Dose 2 (**Final Dose**) at least 8 weeks after Dose 1
	1	Dose 1 was given **before** 12 months of age	It has been at least 4 weeks since Dose 1	Give Dose 2 today	Give Dose 3 (**Final Dose**) at least 8 weeks after Dose 2
			It has **not** been 4 weeks since Dose 1	No dose today	Give Dose 2 at least 4 weeks after Dose 1
		Dose 1 was given at 12 months of age or older	It has been at least 8 weeks since Dose 1	Give Dose 2 (**Final Dose**) today	**No additional doses needed**
			It has **not** been 8 weeks since Dose 1	No dose today	Give Dose 2 (**Final Dose**) at least 8 weeks after Dose 1
	2	Dose 1 was given **before** 12 months of age	It has been at least 8 weeks since Dose 2	Give Dose 3 (**Final Dose**) today	**No additional doses needed**
			It has **not** been 8 weeks since Dose 2	No dose today	Give Dose 3 (**Final Dose**) at least 8 weeks after Dose 2
		Dose 1 was given at 12 months of age or older	→	No dose today	**No additional doses needed**

[1] Refer to notes of the Recommended Child and Adolescent Immunization Schedule for Ages 18 Years or Younger–United States, 2021, for immunization guidance for children at increased risk for *Haemophilus influenzae* type b disease.

Reference: Recommended Child and Adolescent Immunization Schedule for Ages 18 Years or Younger–United States, 2021. www.cdc.gov/vaccines/schedules/downloads/child/0-18yrs-child-combined-schedule.pdf

Catch-Up Guidance for Healthy[1] Children 4 Months through 4 Years of Age

Haemophilus influenzae type b Vaccines: PedvaxHIB Vaccine Only

IF current age is	AND # of previous doses is	AND	AND	AND	THEN	Next dose due
15 through 59 months	0	→	→	→	Give Dose 1 (**Final Dose**) today	**No additional doses needed**
	1	Dose 1 was given **before** 12 months of age	→	→	Give Dose 2 (**Final Dose**) today	**No additional doses needed**
		Dose 1 was given at 12 through 14 months of age	It has been at least 8 weeks since Dose 1	→	Give Dose 2 (**Final Dose**) today	**No additional doses needed**
			It has **not** been 8 weeks since Dose 1	→	No dose today	Give Dose 2 (**Final Dose**) at least 8 weeks after Dose 1
		Dose 1 was given at 15 months of age or older	→	→	No dose today	**No additional doses needed**
	2	Dose 1 was given **before** 12 months of age	Dose 2 was given **before** 15 months of age	It has been at least 8 weeks since Dose 2	Give Dose 3 (**Final Dose**) today	**No additional doses needed**
				It has **not** been 8 weeks since Dose 2	No dose today	Give dose 3 (**Final Dose**) at least 8 weeks after Dose 2
			Dose 2 was given at 15 months of age or older	→	No dose today	**No additional doses needed**
		Dose 1 was given at 12 months or older	→	→	No dose today	**No additional doses needed**

[1] Refer to notes of the Recommended Child and Adolescent Immunization Schedule for Ages 18 Years or Younger–United States, 2021, for immunization guidance for children at increased risk for *Haemophilus influenzae* type b disease.

Reference: Recommended Child and Adolescent Immunization Schedule for Ages 18 Years or Younger–United States, 2021. www.cdc.gov/vaccines/schedules/downloads/child/0-18yrs-child-combined-schedule.pdf

Catch-Up Guidance for Children 4 Months through 17 Years of Age

Inactivated Polio Vaccine (IPV)

The table below provides guidance for children whose vaccinations have been delayed. Start with the child's age and information on previous doses (previous doses must be documented and must meet minimum age requirements and minimum intervals between doses). Use this table in conjunction with table 2 of the Recommended Child and Adolescent Immunization Schedule for Ages 18 Years or Younger, found at www.cdc.gov/vaccines/schedules/hcp/child-adolescent.html.

IF current age is	AND # of previous doses[1] is	AND		THEN	Next dose due[2]
4 through 18 months	Unknown or 0	→		Give Dose 1 today	Give Dose 2 at least 4 weeks after Dose 1
	1	It has been at least 4 weeks since Dose 1		Give Dose 2 today	Give Dose 3 at least 4 weeks after Dose 2 **and** at 6 months of age or older
		It has **not** been at least 4 weeks since Dose 1		No dose today	Give Dose 2 at least 4 weeks after Dose 1
	2	It has been at least 4 weeks since Dose 2	Child is 6 months of age or older	Give Dose 3 today	Give Dose 4 (**Final Dose**) at 4 through 6 years of age
			Child is younger than 6 months of age	No dose today	Give Dose 3 at 6 months of age
		It has **not** been at least 4 weeks since Dose 2	→	No dose today	Give Dose 3 at least 4 weeks after Dose 2 **and** at 6 months of age or older
19 months through 3 years	Unknown or 0	→		Give Dose 1 today	Give Dose 2 at least 4 weeks after Dose 1
	1	It has been at least 4 weeks since Dose 1		Give Dose 2 today	Give Dose 3 at least 4 weeks after Dose 2
		It has **not** been at least 4 weeks since Dose 1		No dose today	Give Dose 2 at least 4 weeks after Dose 1
	2	It has been at least 4 weeks since Dose 2		Give Dose 3 today	Give Dose 4 (**Final Dose**) at least 6 months after Dose 3 **and** at 4 through 6 years of age
		It has **not** been 4 weeks since Dose 2		No dose today	Give Dose 3 at least 4 weeks after Dose 2

[1] Series containing oral polio vaccine (OPV), either mixed OPV-IPV or OPV only: Total number of doses needed to complete the series is the same as that recommended for the U.S. IPV schedule. www.cdc.gov/mmwr/volumes/66/wr/mm6601a6.htm

[2] Next dose due is not the final dose in the series unless explicitly stated.

Reference: Recommended Child and Adolescent Immunization Schedule for Ages 18 Years or Younger—United States, 2021. www.cdc.gov/vaccines/schedules/downloads/child/0-18yrs-child-combined-schedule.pdf

Revised February 2021

Catch-Up Guidance for Children 4 Months through 17 Years of Age

Inactivated Polio Vaccine (IPV)

IF current age is	AND # of previous doses[1] is	AND			THEN	Next dose due2
4 through 17 years	Unknown or 0	→			Give Dose 1 today	Give Dose 2 at least 4 weeks after Dose 1
	1	It has been at least 4 weeks since Dose 1			Give Dose 2 today	Give Dose 3 (**Final Dose**) at least 6 months after Dose 2
		It has **not** been 4 weeks since Dose 1			No dose today	Give Dose 2 at least 4 weeks after Dose 1
	2	It has been at least 6 months since Dose 2			Give Dose 3 (**Final Dose**) today	**No additional doses needed**
		It has **not** been 6 months since Dose 2			No dose today	Give Dose 3 (**Final Dose**) at least 6 months after Dose 2
	3	Dose 3 was given **before** 4 years of age	It has been at least 6 months since Dose 3	→	Give Dose 4 (**Final dose**) today	**No additional doses needed**
			It has **not** been at least 6 months since Dose 3	→	No dose today	Give Dose 4 (**Final Dose**) at least 6 months after Dose 3
		Dose 3 was given at 4 years of age or older	Dose 3 was given at least 6 months from previous dose	→	No dose today	**No additional doses needed**
			Dose 3 was **not** given at least 6 months from previous dose	It has been at least 6 months since Dose 3	Give Dose 4 (**Final dose**) today	**No additional doses needed**
				It has **not** been at least 6 months since Dose 3	No dose today	Give Dose 4 (**Final Dose)** at least 6 months after Dose 3

[1] Series containing oral polio vaccine (OPV), either mixed OPV-IPV or OPV only: Total number of doses needed to complete the series is the same as that recommended for the U.S. IPV schedule. www.cdc.gov/mmwr/volumes/66/wr/mm6601a6.htm

[2] Next dose due is not the final dose in the series unless explicitly stated.

Reference: Recommended Child and Adolescent Immunization Schedule for Ages 18 Years or Younger—United States, 2021. www.cdc.gov/vaccines/schedules/downloads/child/0-18yrs-child-combined-schedule.pdf

Catch-Up Guidance for Healthy[1] Children 4 Months through 4 Years of Age

Pneumococcal Conjugate Vaccine: PCV

The table below provides guidance for children whose vaccinations have been delayed. Start with the child's age and information on previous doses (previous doses must be documented and must meet minimum age requirements and minimum intervals between doses). Use this table in conjunction with table 2 of the Recommended Child and Adolescent Immunization Schedule for Ages 18 Years or Younger, found at www.cdc.gov/vaccines/schedules/hcp/child-adolescent.html.

IF current age is	AND # of previous doses is	AND		THEN	Next dose due
4 through 6 months	0 or unknown	→	→	Give Dose 1 today	Give Dose 2 at least 4 weeks after Dose 1
	1	→	It has been at least 4 weeks since Dose 1	Give Dose 2 today	Give Dose 3 at least 4 weeks after Dose 2
		→	It has **not** been at least 4 weeks since Dose 1	No dose today	Give Dose 2 at least 4 weeks after Dose 1
	2	→	It has been at least 4 weeks since Dose 2	Give Dose 3 today	Give Dose 4 (**Final Dose**) at 12 months of age or older
		→	It has **not** been at least 4 weeks since Dose 2	No dose today	Give Dose 3 at least 4 weeks after Dose 2
7 through 11 months	0	→	→	Give Dose 1 today	Give Dose 2 at least 4 weeks after Dose 1
	1	Dose 1 was given **before** 7 months of age	It has been at least 4 weeks since Dose 1	Give Dose 2 today	Give Dose 3 (**Final Dose**) at least 8 weeks after Dose 2 **and** at 12 months of age or older
			It has **not** been 4 weeks since Dose 1	No dose today	Give Dose 2 at least 4 weeks after Dose 1
		Dose 1 was given at 7 months or older	It has been at least 4 weeks since Dose 1	Give Dose 2 today	Give Dose 3 (**Final Dose**) at least 8 weeks after Dose 2 **and** at 12 months of age or older
			It has **not** been 4 weeks since Dose 1	No dose today	Give Dose 2 at least 4 weeks after Dose 1
	2	Dose 2 was given **before** 7 months of age	It has been at least 4 weeks since Dose 2	Give Dose 3 today	Give Dose 4 (**Final Dose**) at least 8 weeks after Dose 3 **and** at 12 months of age or older
			It has **not** been 4 weeks since Dose 2	No dose today	Give Dose 3 at least 4 weeks after Dose 2
		Dose 2 was given at 7 months or older	→	No dose today	Give Dose 3 (**Final Dose**) at least 8 weeks after Dose 2 **and** at 12 months of age or older

[1] Refer to the notes of the Recommended Child and Adolescent Immunization Schedule for Ages 18 Years or Younger–United States, 2021, for immunization guidance for children at increased risk for pneumococcal disease.

Reference: Recommended Child and Adolescent Immunization Schedule for Ages 18 Years or Younger–United States, 2021. www.cdc.gov/vaccines/schedules/downloads/child/0-18yrs-child-combined-schedule.pdf.

Revised February 2021

Catch-Up Guidance for Healthy[1] Children 4 Months through 4 Years of Age

Pneumococcal Conjugate Vaccine: PCV

The table below provides guidance for children whose vaccinations have been delayed. Start with the child's age and information on previous doses (previous doses must be documented and must meet minimum age requirements and minimum intervals between doses). Use this table in conjunction with table 2 of the Recommended Child and Adolescent Immunization Schedule for Ages 18 Years or Younger, found at www.cdc.gov/vaccines/schedules/hcp/child-adolescent.html.

IF current age is	AND # of previous doses is	AND	AND	THEN	Next dose due
12 through 23 months	0 or unknown	→	→	Give Dose 1 today	Give Dose 2 (**Final Dose**) at least 8 weeks after Dose 1
	1	Dose 1 was given **before** 12 months of age	It has been at least 4 weeks since Dose 1	Give Dose 2 today	Give Dose 3 (**Final Dose**) at least 8 weeks after Dose 2
			It has **not** been 4 weeks since Dose 1	No dose today	Give Dose 2 at least 4 weeks after Dose 1
		Dose 1 was given at 12 months of age or older	It has been at least 8 weeks since Dose 1	Give Dose 2 (**Final Dose**) today	**No additional doses needed**
			It has **not** been 8 weeks since Dose 1	No dose today	Give Dose 2 (**Final Dose**) at least 8 weeks after Dose 1
	2	Both doses were given **before** 12 months of age	It has been at least 8 weeks since Dose 2	Give Dose 3 (**Final Dose**) today	N**o additional doses needed**
			It has **not** been 8 weeks since Dose 2	No dose today	Give Dose 3 (**Final Dose**) at least 8 weeks after Dose 2
		At least one dose was given at 12 months or older	It has been at least 8 weeks since Dose 2	Give Dose 3 (**Final Dose**) today	**No additional doses needed**
			It has **not** been 8 weeks since Dose 2	No dose today	Give Dose 3 (**Final Dose**) at least 8 weeks after Dose 2
		Both doses were given at 12 months or older[2]	→	No dose today	**No additional doses needed**
	3	All doses were given **before** 12 months of age	It has been at least 8 weeks since Dose 3	Give Dose 4 (**Final Dose**) today	**No additional doses needed**
			It has **not** been 8 weeks since Dose 3	No dose today	Give Dose 4 (**Final Dose**) at least 8 weeks after Dose 3
		1 or more doses were given at 12 months of age or older	→	No dose today	**No additional doses needed**

[1] Refer to the notes of the Recommended Child and Adolescent Immunization Schedule for Ages 18 Years or Younger–United States, 2021, for immunization guidance for children at increased risk for pneumococcal disease.

[2] Separated by at least 8 weeks.

Reference: Recommended Child and Adolescent Immunization Schedule for Ages 18 Years or Younger–United States, 2021. www.cdc.gov/vaccines/schedules/downloads/child/0-18yrs-child-combined-schedule.pdf.

Catch-Up Guidance for Healthy[1] Children 4 Months through 4 Years of Age

Pneumococcal Conjugate Vaccine: PCV

IF current age is	AND # of previous doses is	AND	AND	AND	THEN	Next dose due
24 through 59 months	0	→	→	→	Give Dose 1 today	**No additional doses needed**
	1	Dose 1 was given **before** 1st birthday	→	→	Give Dose 2 (**Final Dose**) today	**No additional doses needed**
		Dose 1 was given **after** 1st birthday	Dose 1 was given **before** 2nd birthday	It has been at least 8 weeks since Dose 1	Give Dose 2 **(Final Dose)** today	**No additional doses needed**
				It has **not** been at least 8 weeks since Dose 1	No dose today	Give Dose 2 **(Final Dose)** at least 8 weeks after Dose 1
			Dose 1 was given **after** 2nd birthday	→	No dose today	**No additional doses needed**
	2	Dose 1 was given **before** 12 months of age	Dose 2 was given **before** 1st birthday	→	Give Dose 3 (**Final Dose**) today	**No additional doses needed**
			Dose 2 was given **after** 1st birthday	Dose 2 was given **before** 2nd birthday	Give Dose 3 (**Final Dose**) today	**No additional doses needed**
				Dose 2 was given **after** 2nd birthday	No dose today	**No additional doses needed**
		Dose 1 was given **after** 12 months of age	→	→	No dose today	**No additional doses needed**
	3	All 3 doses were given **before** 12 months of age	→	→	Give Dose 4 (**Final Dose**) today	**No additional doses needed**
		1 or more doses were given at 12 months or older	→	→	No dose today	**No additional doses needed**

A

[1] Refer to the notes of the Recommended Child and Adolescent Immunization Schedule for Ages 18 Years or Younger–United States, 2021, for immunization guidance for children at increased risk for pneumococcal disease.

Reference: Recommended Child and Adolescent Immunization Schedule for Ages 18 Years or Younger–United States, 2021. www.cdc.gov/vaccines/schedules/downloads/child/0-18yrs-child-combined-schedule.pdf.

Catch-Up Guidance for Children 7 through 9 Years of Age

Tetanus-, Diphtheria-, and Pertussis-Containing Vaccines: Tdap/Td[1]

The table below provides guidance for children whose vaccinations have been delayed. Start with the child's age and information on previous doses (previous doses must be documented and must meet minimum age requirements and minimum intervals between doses). Use this table in conjunction with table 2 of the Recommended Child and Adolescent Immunization Schedule for Ages 18 Years or Younger, found at www.cdc.gov/vaccines/schedules/hcp/child-adolescent.html.

IF current age is	AND # of previous doses of DTaP, DT, Td, or Tdap is	AND	AND	AND	THEN	Next dose due
7 through 9 years[1]	Unknown or 0	→	→	→	Give Dose 1 (Tdap) today	Give Dose 2 (Td or Tdap) at least 4 weeks after Dose 1
	1	Dose 1 was given **before** 12 months of age	→	→	Give Dose 2 (Tdap) today	Give Dose 3 (Td or Tdap) at least 4 weeks after Dose 2
		Dose 1 was given at 12 months of age or older	It has been at least 4 weeks since Dose 1	Dose 1 was Tdap	Give Dose 2 (Td or Tdap) today	Give Dose 3 (Td or Tdap) at least 6 calendar months after Dose 2
				Dose 1 was **not** Tdap	Give Dose 2 (Tdap) today	
			It has **not** been 4 weeks since Dose 1	Dose 1 was Tdap	No dose today	Give Dose 2 (Td or Tdap) at least 4 weeks after Dose 1
				Dose 1 was **not** Tdap	No dose today	Give Dose 2 (Tdap) at least 4 weeks after Dose 1
	2	Dose 1 was given **before** 12 months of age	It has been at least 4 weeks since Dose 2	Dose 2 was Tdap[1]	Give Dose 3 (Td or Tdap) today	Give Dose 4 (Td or Tdap) at least 6 calendar months after Dose 3
				No dose was Tdap	Give Dose 3 (Tdap) today	
			It has **not** been 4 weeks since Dose 2	Dose 2 was Tdap	No dose today	Give Dose 3 (Td or Tdap) at least 4 weeks after Dose 2
				No dose was Tdap	No dose today	Give Dose 3 (Tdap) at least 4 weeks after Dose 2
		Dose 1 was given at 12 months of age or older	It has been at least 6 calendar months since Dose 2	Any dose was Tdap[1]	Give Dose 3 (Td or Tdap) today	Give Tdap at 11–12 years of age[1,2]
				No dose was Tdap	Give Dose 3 (Tdap) today	
			It has **not** been 6 calendar months since Dose 2	Any dose was Tdap[1]	No dose today	Give Dose 3 (Td or Tdap) at least 6 calendar months after Dose 2[1]
				No dose was Tdap	No dose today	Give Dose 3 (Tdap) at least 6 calendar months after Dose 2

[1]For persons 7-9 years of age who receive a dose of Tdap, the routine adolescent Tdap dose should be administered at age 11-12.

[2]Tdap may be administered regardless of the interval since the last tetanus- and diphtheria-toxoid-containing vaccine.

Reference: Recommended Child and Adolescent Immunization Schedule for Ages 18 Years or Younger—United States, 2021. www.cdc.gov/vaccines/schedules/downloads/child/0-18yrs-child-combined-schedule.pdf.

Catch-Up Guidance for Children 7 through 9 Years of Age

Tetanus-, Diphtheria-, and Pertussis-Containing Vaccines: Tdap/Td[1]

IF current age is	AND # of previous doses of DTaP, DT, Td, or Tdap is	AND	AND	AND	THEN	Next dose due
7 through 9 years[1]	3	Dose 1 was given **before** 12 months of age	It has been at least 6 calendar months since Dose 3	Any dose was Tdap[1]	Give Dose 4 (Td or Tdap) today	Give Tdap at 11–12 years of age[1,2]
				No dose was Tdap	Give Dose 4 (Tdap) today	
			It has **not** been 6 calendar months since Dose 3	Any dose was Tdap[1]	No dose today	Give Dose 4 (Td or Tdap) at least 6 calendar months after Dose 3[1]
				No dose was Tdap	No dose today	Give Dose 4 (Tdap) at least 6 calendar months after Dose 3[1]
		Dose 1 was given at 12 months of age or older	No dose was Tdap	→	Give Dose 4 (Tdap) today[2]	Give Tdap at 11–12 years of age[1,2]
			Any dose was Tdap	→	No dose today	Give Tdap at 11–12 years of age[1,2]
	4	→	Dose of DTaP or Tdap given after 4th birthday	→	No dose today	Give Tdap at 11–12 years of age[1,2]
			No DTaP or Tdap given after 4th birthday	→	Give a dose of Tdap today	

[1]For persons 7-9 years of age who receive a dose of Tdap, the routine adolescent Tdap dose should be administered at age 11-12.

[2]Tdap may be administered regardless of the interval since the last tetanus- and diphtheria-toxoid-containing vaccine.

Reference: Recommended Child and Adolescent Immunization Schedule for Ages 18 Years or Younger—United States, 2021.

www.cdc.gov/vaccines/schedules/downloads/child/0-18yrs-child-combined-schedule.pdf

Revised February 2021

Catch-Up Guidance for Children 10 through 18 Years of Age

Tetanus-, Diphtheria-, and Pertussis-Containing Vaccines: Tdap/Td[1]

The table below provides guidance for children whose vaccinations have been delayed. Start with the child's age and information on previous doses (previous doses must be documented and must meet minimum age requirements and minimum intervals between doses). Use this table in conjunction with table 2 of the Recommended Child and Adolescent Immunization Schedule for Ages 18 Years or Younger, found at www.cdc.gov/vaccines/schedules/hcp/child-adolescent.html.

IF current age is	AND # of previous doses of DTaP, DT, Td, or Tdap is	AND	AND	AND	THEN	Next dose due
10 through 18 years	Unknown or 0	→	→	→	Give Dose 1 (Tdap) today	Give Dose 2 (Td or Tdap) at least 4 weeks after Dose 1
	1	Dose 1 was given **before** 12 months of age	→	→	Give Dose 2 (Tdap) today	Give Dose 3 (Td or Tdap) at least 4 weeks after Dose 2
		Dose 1 was given at 12 months of age or older	It has been at least 4 weeks since Dose 1	Dose 1 was Tdap	Give Dose 2 (Td or Tdap) today	Give Dose 3 (Td or Tdap) at least 6 calendar months after Dose 2
				Dose 1 was **not** Tdap	Give Dose 2 (Tdap) today	
			It has **not** been 4 weeks since Dose 1	Dose 1 was Tdap	No dose today	Give Dose 2 (Td or Tdap) at least 4 weeks after Dose 1
				Dose 1 was **not** Tdap	No dose today	Give Dose 2 (Tdap) at least 4 weeks after Dose 1
	2	Dose 1 was given **before** 12 months of age	It has been at least 4 weeks since Dose 2	Any dose was Tdap[1]	Give Dose 3 (Td or Tdap) today[2]	Give Dose 4 (Td or Tdap) at least 6 calendar months after Dose 3
				No dose was Tdap[3]	Give Dose 3 (Tdap) today	
			It has **not** been 4 weeks since Dose 2	Any dose was Tdap[1]	No dose today	Give Dose 3 (Td or Tdap) at least 4 weeks after Dose 2[2]
				No dose was Tdap[3]	No dose today	Give Dose 3 (Tdap) at least 4 weeks after Dose 2
		Dose 1 was given at 12 months of age or older	It has been at least 6 calendar months since Dose 2	Any dose was Tdap[1]	Give Dose 3 (Td or Tdap) today[2]	Give Td or Tdap 10 years after Dose 3
				No dose was Tdap[2]	Give Dose 3 (Tdap) today	
			It has **not** been 6 calendar months since Dose 2	Any dose was Tdap[1]	No dose today	Give Dose 3 (Td or Tdap) at least 6 calendar months after Dose 2[2]
				No dose was Tdap[3]	No dose today	Give Dose 3 (Tdap) at least 6 calendar months after Dose 2

[1]Given at 10 years of age or older.

2If the previous Tdap dose(s) was administered before the 10th birthday, then a dose of Tdap is recommended now.

[3]Or Tdap administered at 9 years of age or younger.

Reference: Recommended Child and Adolescent Immunization Schedule for Ages 18 Years or Younger—United States, 2021. www.cdc.gov/vaccines/schedules/downloads/child/0-18yrs-child-combined-schedule.pdf

Catch-Up Guidance for Children 10 through 18 Years of Age

Tetanus-, Diphtheria-, and Pertussis-Containing Vaccines: Tdap/Td[1]

IF current age is	AND # of previous doses of DTaP, DT, Td, or Tdap is	AND	AND	AND	THEN	Next dose due
10 through 18 years	3	Dose 1 was given **before** 12 months of age	It has been at least 6 calendar months since Dose 3	Any dose was Tdap[1]	Give Dose 4 (Td or Tdap) today[2]	Give Td or Tdap 10 years after Dose 4
				No dose was Tdap[3]	Give Dose 4 (Tdap) today	
			It has **not** been 6 calendar months since Dose 3	Any dose was Tdap[1]	No dose today	Give Dose 4 (Td or Tdap) at least 6 calendar months after Dose 3[2]
				No dose was Tdap[3]	No dose today	Give Dose 4 (Tdap) at least 6 calendar months after Dose 3
		Dose 1 was given at 12 months of age or older	No dose was Tdap[1]	→	Give Dose 4 (Tdap) today	Give Td or Tdap 10 years after Dose 4
			Any dose was Tdap[2]	→	No dose today	Give Td or Tdap 10 years after Dose 3
	4	→	No Tdap was given after 7th birthday	→	Give a dose of Tdap today[4]	Give Td or Tdap 10 years after Tdap dose
			Any dose of Tdap was given at age 7 years or older[1]	No Tdap was given after 10th birthday		
				Tdap was given after 10th birthday	No dose today	Give Td or Tdap 10 years after Dose 4

[1]Given at 10 years of age or older.

[2]If the previous Tdap dose(s) was administered before the 10th birthday, then a dose of Tdap is recommended now.

[3]Or Tdap administered at 9 years of age or younger.

[4]The preferred age at administration for this dose is 11–12 years. However, if Tdap is administered at age 10 years, the Tdap dose may count as the adolescent Tdap dose.

Reference: Recommended Child and Adolescent Immunization Schedule for Ages 18 Years or Younger—United States, 2021.
www.cdc.gov/vaccines/schedules/downloads/child/0-18yrs-child-combined-schedule.pdf

Healthcare Personnel Vaccination Recommendations[1]

VACCINES AND RECOMMENDATIONS IN BRIEF

Hepatitis B – If previously unvaccinated, give a 2-dose (Heplisav-B) or 3-dose (Engerix-B or Recombivax HB) series. Give intramuscularly (IM). For HCP who perform tasks that may involve exposure to blood or body fluids, obtain anti-HBs serologic testing 1–2 months after dose #2 (for Heplisav-B) or dose #3 (for Engerix-B or Recombivax HB).

Influenza – Give 1 dose of influenza vaccine annually. Inactivated injectable vaccine is given IM. Live attenuated influenza vaccine (LAIV) is given intranasally.

MMR – For healthcare personnel (HCP) born in 1957 or later without serologic evidence of immunity or prior vaccination, give 2 doses of MMR, 4 weeks apart. For HCP born prior to 1957, see below. Give subcutaneously (Subcut).

Varicella (chickenpox) – For HCP who have no serologic proof of immunity, prior vaccination, or diagnosis or verification of a history of varicella or herpes zoster (shingles) by a healthcare provider, give 2 doses of varicella vaccine, 4 weeks apart. Give Subcut.

Tetanus, diphtheria, pertussis – Give 1 dose of Tdap as soon as feasible to all HCP who have not received Tdap previously and to pregnant HCP with each pregnancy (see below). Give Td or Tdap boosters every 10 years thereafter. Give IM.

Meningococcal – Give both MenACWY and MenB to microbiologists who are routinely exposed to isolates of *Neisseria meningitidis*. As long as risk continues: boost with MenB after 1 year, then every 2–3 years thereafter; boost with MenACWY every 5 years. Give MenACWY and MenB IM.

Hepatitis A, typhoid, and polio vaccines are not routinely recommended for HCP who may have on-the-job exposure to fecal material.

Hepatitis B

Unvaccinated healthcare personnel (HCP) and/or those who cannot document previous vaccination should receive either a 2-dose series of Heplisav-B at 0 and 1 month or a 3-dose series of either Engerix-B or Recombivax HB at 0, 1, and 6 months. HCP who perform tasks that may involve exposure to blood or body fluids should be tested for hepatitis B surface antibody (anti-HBs) 1–2 months after dose #2 of Heplisav-B or dose #3 of Engerix-B or Recombivax HB to document immunity.

- If anti-HBs is at least 10 mIU/mL (positive), the vaccinee is immune. No further serologic testing or vaccination is recommended.
- If anti-HBs is less than 10 mIU/mL (negative), the vaccinee is not protected from hepatitis B virus (HBV) infection, and should receive another 2-dose or 3-dose series of HepB vaccine on the routine schedule, followed by anti-HBs testing 1–2 months later. A vaccinee whose anti-HBs remains less than 10 mIU/mL after 2 complete series is considered a "non-responder."

For non-responders: HCP who are non-responders should be considered susceptible to HBV and should be counseled regarding precautions to prevent HBV infection and the need to obtain HBIG prophylaxis for any known or probable parenteral exposure to hepatitis B surface antigen (HBsAg)-positive blood or blood with unknown HBsAg status. It is also possible that non-responders are people who are HBsAg positive. HBsAg testing is recommended. HCP found to be HBsAg positive should be counseled and medically evaluated.

For HCP with documentation of a complete 2-dose (Heplisav-B) or 3-dose (Engerix-B or Recombivax HB) vaccine series but no documentation of anti-HBs of at least 10 mIU/mL (e.g., those vaccinated in childhood): HCP who are at risk for occupational blood or body fluid exposure might undergo anti-HBs testing upon hire or matriculation. See references 2 and 3 for details.

Influenza

All HCP, including physicians, nurses, paramedics, emergency medical technicians, employees of nursing homes and chronic care facilities, students in these professions, and volunteers, should receive annual vaccination against influenza. Live attenuated influenza vaccine (LAIV) may be given only to non-pregnant healthy HCP age 49 years and younger. Inactivated injectable influenza vaccine (IIV) is preferred over LAIV for HCP who are in close contact with severely immunosuppressed patients (e.g., stem cell transplant recipients) when they require protective isolation.

Measles, Mumps, Rubella (MMR)

HCP who work in medical facilities should be immune to measles, mumps, and rubella.

- HCP born in 1957 or later can be considered immune to measles, mumps, or rubella only if they have documentation of (a) laboratory confirmation of disease or immunity or (b) appropriate vaccination against measles, mumps, and rubella (i.e., 2 doses of live measles and mumps vaccines given on or after the first birthday and separated by 28 days or more, and at least 1 dose of live rubella vaccine). HCP with 2 documented doses of MMR are not recommended to be serologically tested for immunity; but if they are tested and results are negative or equivocal for measles, mumps, and/or rubella, these HCP should be considered to have presumptive evidence of immunity to measles, mumps, and/or rubella and are not in need of additional MMR doses.
- Although birth before 1957 generally is considered acceptable evidence of measles, mumps, and rubella immunity, 2 doses of MMR vaccine should be considered for unvaccinated HCP born before 1957 who do not have laboratory evidence of disease or immunity to measles and/or mumps. One dose of MMR vaccine should be considered for HCP with no laboratory evidence of disease or immunity to rubella. For these same HCP who do not have evidence of immunity, 2 doses of MMR vaccine are recommended during an outbreak of measles or mumps and 1 dose during an outbreak of rubella.

Varicella

It is recommended that all HCP be immune to varicella. Evidence of immunity in HCP includes documentation of 2 doses of varicella vaccine given at least 28 days apart, laboratory evidence of immunity, laboratory confirmation of disease, or diagnosis or verification of a history of varicella or herpes zoster (shingles) by a healthcare provider.

Tetanus/Diphtheria/Pertussis (Td/Tdap)

All HCPs who have not or are unsure if they have previously received a dose of Tdap should receive a dose of Tdap as soon as feasible, without regard to the interval since the previous dose of Td. Pregnant HCP should be revaccinated during each pregnancy. All HCPs should then receive Td or Tdap boosters every 10 years thereafter.

Meningococcal

Vaccination with MenACWY and MenB is recommended for microbiologists who are routinely exposed to isolates of *N. meningitidis*. The two vaccines may be given concomitantly but at different anatomic sites, if feasible.

REFERENCES

1 CDC. Immunization of Health-Care Personnel: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR*, 2011; 60(RR-7).

2 CDC. Prevention of Hepatitis B Virus Infection in the United States. Recommendations of the Advisory Committee on Immunization Practices. *MMWR*, 2018; 67(RR1):1–30.

3 IAC. Pre-exposure Management for Healthcare Personnel with a Documented Hepatitis B Vaccine Series Who Have Not Had Post-vaccination Serologic Testing. Accessed at www.immunize.org/catg.d/p2108.pdf.

For additional specific ACIP recommendations, visit CDC's website at www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/index.html or visit IAC's website at www.immunize.org/acip.

Appendix A

Recommended and minimum ages and intervals between vaccine doses[a],[b],[c],[d]

Vaccine and dose number	Recommended age for this dose	Minimum age for this dose	Recommended interval to next dose	Minimum interval to next dose
DTaP-1[e]	2 months	6 weeks	8 weeks	4 weeks
DTaP-2	4 months	10 weeks	8 weeks	4 weeks
DTaP-3	6 months	14 weeks	6-12 months[f]	6 months[f]
DTaP-4	15-18 months	15 months[f]	3 years	6 months
DTaP-5[g]	4-6 years	4 years	—	—
HepA-1[e]	12-23 months	12 months	6-18 months	6 months
HepA-2	≥18 months	18 months	—	—
HepB-1[h]	Birth	Birth	4 weeks-4 months	4 weeks
HepB-2	1-2 months	4 weeks	8 weeks-17 months	8 weeks
HepB-3[i]	6-18 months	24 weeks	—	—
Hib-1[j]	2 months	6 weeks	8 weeks	4 weeks
Hib-2	4 months	10 weeks	8 weeks	4 weeks
Hib-3[k]	6 months	14 weeks	6-9 months	8 weeks
Hib-4	12-15 months	12 months	—	—
HPV-1 (Two-Dose Series)[l]	11-12 years	9 years	6 months	5 months
HPV-2	11-12 years (+6 months)	9 years +5 months[m]	—	—
HPV-1[n] **(Three-Dose Series)**	11-12 years	9 years	1-2 months	4 weeks
HPV-2	11-12 years (+1-2 months)	9 years (+4 weeks)	4 months	12 weeks[n]
HPV-3[n]	11-12 years (+6 months)	9 years (+5 months)	—	—
Influenza, inactivated[o]	≥6 months	6 months[p]	4 weeks	4 weeks
IPV-1[e]	2 months	6 weeks	8 weeks	4 weeks
IPV-2	4 months	10 weeks	8 weeks-14 months	4 weeks
IPV-3	6-18 months	14 weeks	3-5 years	6 months
IPV-4[q]	4-6 years	4 years	—	—
LAIV[o]	2-49 years	2 years	4 weeks	4 weeks
MenACWY-1[r]	11-12 years	2 months[s]	4-5 years	8 weeks
MenACWY-2	16 years	11 years (+ 8 weeks)[t]	—	—
MenB-1	Healthy adolescents: 16-23 years	16 years	Bexsero: 4 weeks Trumenba: 6 months[c]	Bexsero: 4 weeks Trumenba: 6 months[c]
MenB-1	Persons at increased risk: ≥10 years	10 years	Bexsero: 4 weeks Trumenba: 1–2 months[c]	Bexsero: 4 weeks Trumenba: 1 month
MenB-2	Healthy adolescents: 16-23 years (+1 month)	16 years (+1 month)	—	—
MenB-2	Persons at increased risk: ≥10 years (+1 month)	10 years (+1 month)	Bexsero: — Trumenba: 4-5 month[c]	Bexsero: — Trumenba: 4 months[c]
MenB-3[u]	Persons at increased risk: ≥10 years (+6 months[c])	10 years (+6 months[c])	—	—

Vaccine and dose number	Recommended age for this dose	Minimum age for this dose	Recommended interval to next dose	Minimum interval to next dose
MMR-1[v]	12-15 months	12 months	3-5 years	4 weeks
MMR-2[v]	4-6 years	13 months	—	—
PCV13-1[j]	2 months	6 weeks	8 weeks	4 weeks
PCV13-2	4 months	10 weeks	8 weeks	4 weeks
PCV13-3	6 months	14 weeks	6 months	8 weeks
PCV13-4	12-15 months	12 months	—	—
PPSV23-1	—	2 years	5 years	5 years
PPSV23-2[w]	—	7 years	—	—
Rotavirus-1[x]	2 months	6 weeks	8 weeks	4 weeks
Rotavirus-2	4 months	10 weeks	8 weeks	4 weeks
Rotavirus-3[x]	6 months	14 weeks	—	—
Td	11-12 years	7 years	10 years	5 years
Tdap[y]	≥11 years	7 years	—	—
Varicella-1[v]	12-15 months	12 months	3-5 years	12 weeks[z]
Varicella-2[v]	4-6 years	15 months[aa]	—	—
RZV-1	≥50 years	50 years[bb]	2-6 months	4 weeks
RZV-2	≥50 years (+2-6months)	50 years	—	—

Abbreviations: DTaP = diphtheria and tetanus toxoids and acellular pertussis; HepA = hepatitis A; HepB = hepatitis B; Hib = *Haemophilus influenzae* type b; HPV = human papillomavirus; IPV = inactivated poliovirus; LAIV = live, attenuated influenza vaccine; MenACWY = quadrivalent meningococcal conjugate vaccine; MenB = serogroup B meningococcal vaccine; MMR = measles, mumps, and rubella; MMRV = measles, mumps, rubella, and varicella; PCV13 = pneumococcal conjugate vaccine; PPSV23= pneumococcal polysaccharide vaccine; PRP-OMP = polyribosylribitol phosphate-meningococcal outer membrane protein conjugate; RZV = recombinant zoster vaccine; Td = tetanus and diphtheria toxoids; Tdap = tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis.

[a] Combination vaccines are available. Use of licensed combination vaccines is generally preferred to separate injections of their equivalent component vaccines. When administering combination vaccines, the minimum age for administration is the oldest age for any of the individual components. The minimum interval between doses is equal to the greatest interval of any of the individual components.

[b] Information on travel vaccines, including typhoid, Japanese encephalitis, and yellow fever, is available at https://www.cdc.gov/travel. Information on other vaccines that are licensed in the United States but not distributed, including anthrax and smallpox, is available at http://emergency.cdc.gov/bioterrorism/.

[c] "Months" refers to calendar months.

[d] Within a number range, a hyphen (-) should be read as "through."

[e] Combination vaccines containing the hepatitis B component are available (Twinrix and Pediarix). These vaccines should not be administered to infants aged <6 weeks because of the other vaccine components (i.e., Hib, DTaP, HepA, and IPV).

[f] The minimum recommended age for DTaP-4 is 15 months, with a recommended 6 months from DTaP-3 (the recommended interval between DTaP-3 and DTaP-4 is 6 months). However, DTaP4 need not be repeated if given on or after 12 months of age and at least 4 months after DTaP-3. The 4-day grace period can be applied when validating past doses and can be applied to the minimum age of 12 months and the minimum interval of 4 months between DTaP-3 and DTaP-4. The 4-day grace period can be used when planning doses ahead of time, but should be applied to the minimum age of 15 months and the minimum interval between DTaP-3 and DTaP-4 of 6 months.

[g] If a fourth dose of DTaP is given on or after the fourth birthday, a fifth dose is not needed if the interval between the third dose and fourth dose is at least 6 months.

[h] Adjuvanted Hepatitis B vaccine (HepB-CgG) can be administered to adults 18 years old and older on a two dose schedule, the first and second dose separated by 4 weeks.

[i] HepB-3 should be administered at least 8 weeks after HepB-2 and at least 16 weeks after HepB-1 and should not be administered before age 24 weeks.

[j] For Hib and PCV13, children receiving the first dose of vaccine at age ≥7 months require fewer doses to complete the series.

[k] If PRP-OMP (Pedvax-Hib, Merck Vaccine Division) was administered at ages 2 and 4 months, a dose at age 6 months is not necessary. The final dose has a minimum age of 12 months.

[l] A two-dose schedule of HPV vaccine is recommended for most persons beginning the series between 9 through 14 years of age. See HPV vaccine-specific recommendations for details. www.cdc.gov/mmwr/volumes/65/wr/pdfs/mm6549a5.pdf.

[m] If a patient is eligible for a 2-dose HPV series, and the second dose is given less than four weeks after the first dose, it is an invalid dose. Administer another dose 6-12 months after the first dose. If the second dose is given less than five months after the first dose, but more than four weeks after the first dose, the next dose should be administered at least 12 weeks after the second dose, and at least 6-12 months after the first dose. The 4-day grace period may be used. If the third dose was administered before December 16, 2016, and was administered 12 weeks after the 2nd dose, and 16 weeks after the first dose, it is a valid dose. The 4-day grace period may be used. If the third dose was administered on or after December 16, 2016, and was administered 12 weeks after the 2nd dose and 5 months after the first dose, it is a valid dose. The 4-day grace period may be used.

Appendix A

[n] The minimum age for HPV-3 is based on the baseline minimum age for the first dose (i.e., 9 years) and the minimum interval of 5 months between the first and third dose. If the third dose was administered before December 16, 2016, and was administered 12 weeks after the 2nd dose, and 16 weeks after the first dose, it is a valid dose. The 4-day grace period may be used. If the third dose was administered on or after December 16, 2016, and was administered 12 weeks after the 2nd dose and 5 months after the first dose, it is a valid dose. The 4-day grace period may be used.

[o] One dose of influenza vaccine per season is recommended for most persons. To determine which children younger than 9 years should receive 2 doses in a single season, please see influenza vaccine-specific recommendations https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/flu.html.

[p] The minimum age for inactivated influenza vaccine varies by vaccine manufacturer. See package insert for vaccine-specific minimum ages.

[q] A fourth dose is not needed if the third dose was administered at ≥4 years and at least 6 months after the previous dose.

[r] Revaccination with meningococcal vaccine is recommended for previously vaccinated persons who remain at high risk for meningococcal disease. Cohn AC, MacNeil JR, Clark TA, et al. Prevention and control of meningococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2013;62(RR-2):1-28.

[s] MenACWY-D (Menactra) can be given as young as 9 months for high-risk persons. MenACWY-CRM (Menveo) can be given as young as 2 months for high-risk persons. Hib-MenCY can be given as young as 6 weeks for high-risk persons. Hib-MenCY is given as a 4-dose series at 2 months, 4 months, 6 months and 12-18 months. MenACWY-TT (MenQuadfi) can be given as young as 2 years for high-risk persons.

[t] For routine non-high risk adolescent vaccination, the minimum age for the booster dose is 16 years.

[u] This dose is not necessary if Bexsero is correctly administered, or if Trumenba is correctly administered to healthy adolescents.

[v] Combination MMRV vaccine can be used for children aged 12 months-12 years.

[w] A second dose of PPSV23 5 years after the first dose is recommended for persons aged ≤65 years at highest risk for serious pneumococcal infection and those who are likely to have a rapid decline in pneumococcal antibody concentration. See https://www.cdc.gov/mmwr/volumes/69/rr/rr6909a1.htm.

[x] The first dose of rotavirus must be administered at age 6 weeks through 14 weeks and 6 days. The vaccine series should not be started for infants aged ≥15 weeks, 0 days. Rotavirus should not be administered to children older than 8 months, 0 days of age regardless of the number of doses received between 6 weeks and 8 months, 0 days of age. If 2 doses of Rotarix (GlaxoSmithKline) are administered as age appropriate, a third dose is not necessary.

[y] Only 1 dose of Tdap is recommended. Subsequent doses should be given as Td or Tdap. For management of a tetanus-prone wound in persons who have received a primary series of tetanus-toxoid–containing vaccine, the minimum interval after a previous dose of any tetanus-containing vaccine is 5 years.

[z] A special grace period of 2 months, based on expert opinion, can be applied to the minimum interval of 3 months, when evaluating records retrospectively, which results in an acceptable minimum interval of 4 weeks. An additional 4 days should not be added on to this grace period.

[aa] A special grace period of 2 months, based on expert opinion, can be applied to the minimum age of 15 months when evaluating records retrospectively, which results in an acceptable minimum age of 13 months. An additional 4 days should not be added on to this grace period.

[bb] If a 1st dose of recombinant zoster vaccine is administered to someone 18-49 years of age, the dose does not need to be repeated. A 4 day grace period can be added to the absolute minimum age of 18 years when evaluating records retrospectively.

Adapted from Table 3-1, ACIP General Best Practice Guidelines for Immunization. **January 2021**

Grace Period: Vaccine doses administered ≤4 days before the minimum interval or age are considered valid; however, local or state mandates might supersede this 4-day guideline.

Recommended intervals between administration of antibody-containing products and measles- or varicella-containing vaccine, by product and indication for vaccination

Product/Indication	Dose (mg IgG/kg) and route[a]	Recommended interval before measles- or live varicella-containing vaccine[b] administration
Blood transfusion—RBCs, washed	10 mL/kg, negligible IgG/kg IV	None
Blood transfusion—RBCs, adenine-saline added	10 mL/kg (10 mg IgG/kg) IV	3 months
Blood transfusion—Packed RBCs (hematocrit 65%)[c]	10 mL/kg (60 mg IgG/kg) IV	6 months
Blood transfusion—Whole blood (hematocrit 35%-50%)[c]	10 mL/kg (80-100 mg IgG/kg) IV	6 months
Blood transfusion—Plasma/platelet products	10 mL/kg (160 mg IgG/kg) IV	7 months
Botulinum Immune Globulin Intravenous (Human)	1.0 mL/kg (50 mg IgG/kg) IV	6 months
Cytomegalovirus IGIV	150 mg/kg maximum	6 months
Hepatitis A IG—Contact prophylaxis	0.1 mL/kg (16.5 mg IgG/kg) IM	6 months[d]
Hepatitis A IG—International travel, <1 month stay	0.1 mL/kg (16.5 mg IgG/kg) IM	6 months[d]
Hepatitis A IG—International travel, ≥1 month stay	0.2 mL/kg (33 mg IgG/kg) IM	6 months[d]
Hepatitis B IG	0.06 mL/kg (10 mg IgG/kg) IM	3 months
IGIV—Replacement therapy for immune deficiencies[e]	300-400 mg/kg IV	8 months
IGIV—Immune thrombocytopenic purpura treatment	400 mg/kg IV	8 months
IGIV—Postexposure varicella prophylaxis	400 mg/kg IV	8 months
IGIV—Postexposure measles prophylaxis for immunocompromised contacts	400 mg/kg IV	8 months
IGIV—Immune thrombocytopenic purpura treatment	1000 mg/kg IV	10 months
IGIV—Kawasaki disease	2 g/kg IV	11 months
Measles prophylaxis IG—Standard (i.e., nonimmunocompromised) contact	0.50 mL/kg (80 mg IgG/kg) IM	6 months
Monoclonal antibody to respiratory syncytial virus F protein (e.g., Synagis [MedImmune])[f]	15 mg/kg IM	None
Rabies IG	20 IU/kg (22 mg IgG/kg) IM	4 months
Tetanus IG	250 units (10 mg IgG/kg) IM	3 months
Varicella IG	125 units/10 kg (60-200 mg IgG/kg) IM, maximum 625 units	5 months

Abbreviations: HIV = human immunodeficiency virus; IG = immune globulin; IgG = immune globulin G; IGIV = intravenous immune globulin; mg IgG/kg = milligrams of immune globulin G per kilogram of body weight; IM = intramuscular; IV = intravenous; RBCs = red blood cells.

[a] This table is not intended for determining the correct indications and dosages for using antibody-containing products. Unvaccinated persons might not be protected fully against measles during the entire recommended interval, and additional doses of IG or measles vaccine might be indicated after measles exposure. Concentrations of measles antibody in an IG preparation can vary by manufacturer's lot. Rates of antibody clearance after receipt of an IG preparation also might vary. Recommended intervals are extrapolated from an estimated half-life of 30 days for passively acquired antibody and an observed interference with the immune response to measles vaccine for 5 months after a dose of 80 mg IgG/kg. Sources: Mason W, Takahashi M, Schneider T. Persisting passively acquired measles antibody following gamma globulin therapy for Kawasaki disease and response to live virus vaccination [Abstract 311]. Presented at the 32 meeting of the Interscience Conference on Antimicrobial Agents and Chemotherapy, Los Angeles, California, October, 1992, AND Siber GR, Werner BG, Halsey NA, et al. Interference of immune globulin with measles and rubella immunization. J Pediatr. 1993;122(2):204-211. DOI: 10.1016/S0022-3476(06)80114-9, AND Mason WH, Schneider TL, Takahashi M. Duration of passively acquired measles antibody and response to live virus vaccination allowing gamma globulin therapy for Kawasaki syndrome. Prog Pediatr Cardiol. 1992;1(1):82. DOI: 10.1016/S1058-9813(06)80067-6. The extrapolation is performed by counting months from 80 mg down to (1-3 mg) (e.g. 80 >>> 40 >> >20 >> >10 >>> 5>>>2.5….equal to FIVE intervals) and adding a grace month, so 80 mg values take a "6 month" interval).

[b] Does not include zoster vaccine recombinant because this vaccine is non-live.

[c] Assumes a serum IgG concentration of 16 mg/mL.

[d] The reason the interval is 6 months (and not 4 months) is that the quantity of 16.5 IgG/kg does not reflect the upper ceiling of the quantity of measles IgG in the product.

[e] Measles vaccination is recommended for children with mild or moderate immunosuppression from HIV infection, and varicella vaccination may be considered for children with mild or moderate immunosuppression from HIV infection, but both are contraindicated for persons with severe immunosuppression from HIV or any other immunosuppressive disorder.

[f] Contains antibody only to respiratory syncytial virus.

Adapted from Table 3-5, ACIP General Best Practice Guidelines for Immunization. January 2021

Revised February 2021

Appendix A

Vaccination of persons with primary and secondary immunodeficiencies

Vaccination of persons with primary immunodeficiencies

Primary immunodeficiency	Specific Immunodeficiency	Contraindicated vaccines[a]	Risk-specific recommended vaccines[a]	Effectiveness and comments
B-lymphocyte (humoral)	Severe antibody deficiencies (e.g., X-linked agammaglobulinemia and common variable immunodeficiency)	OPV[b] Smallpox[c] LAIV BCG Ty21a (live typhoid) Yellow fever MMR MMRV	Pneumococcal Hib (children 12-59 months of age)[d]	The effectiveness of any vaccine is uncertain if it depends only on the humoral response (e.g., PPSV23). IGIV interferes with the immune response to measles vaccine and possibly varicella vaccine
	Less severe antibody deficiencies (e.g., selective IgA deficiency and IgG subclass deficiency)	OPV[b] BCG Yellow fever[e] Other live vaccines appear to be safe	Pneumococcal Hib (children 12-59 months of age)[d]	All vaccines likely effective; immune response might be attenuated
T-lymphocyte (cell-mediated and humoral)	Complete defects (e.g., SCID disease, complete DiGeorge syndrome)	All live vaccines[f],[g],[h]	Pneumococcal Hib (children 12-59 months of age)[d]	Vaccines likely to be effective
	Partial defects (e.g., most patients with DiGeorge syndrome, Wiskott-Aldrich syndrome, ataxia-telangiectasia)	All live vaccines[f],[g],[h]	Pneumococcal Meningococcal Hib (children 12-59 months of age)[d]	Effectiveness of any vaccine depends on degree of immune suppression
	Interferon-gamma/ Interleukin 12 axis deficiencies	All live bacterial vaccines (All live vaccines contraindicated in Interferon-gamma or interferon-alpha deficiencies)	None	—
Complement	Persistent complement, properdin, or factor B deficiency	None	Pneumococcal Meningococcal Hib (children 12-59 months of age)[d]	All routine vaccines likely effective
	Taking eculizumab (Soliris) and/or ravulizumab (Ultomiris)	None	Meningococcal	—
Phagocytic function	Chronic granulomatous disease	Live bacterial vaccines[f]	None	Live viral vaccines likely safe and effective
	Phagocytic deficiencies that are undefined or accompanied by defects in T-cell and NK cell dysfunction (such as a Chediak-Higashi syndrome, Leukocyte Adhesion Deficiency [LAD], and myeloperoxidase deficiency)	MMR MMRV Varicella OPV[b] Smallpox BCG LAIV Ty21a Yellow Fever and bacterial vaccines[f],[g]	Pneumococcal	All inactivated vaccines safe and likely effective

Vaccination of persons with secondary immunodeficiencies

Secondary immunodeficiency	Contraindicated vaccines[a]	Risk-specific recommended vaccines[a]	Effectiveness and comments
HIV/AIDS	OPV[b] Smallpox BCG LAIV MMRV Withhold MMR and varicella in severely immunocompromised persons Yellow fever vaccine might have a contraindication or a precaution depending on clinical parameters of immune function[i]	Pneumococcal Hib[d], [j] HepB MenACWY	MMR and Varicella vaccine in those with mild immunosuppression, rotavirus, and all inactivated vaccines, including inactivated influenza as per routine vaccination schedule, might be effective[k]
Generalized malignant neoplasm, transplantation, immunosuppressive or radiation therapy	Live viral and bacterial, depending on immune status[f],[g],[l]	Pneumococcal Hib[m]	Effectiveness of any vaccine depends on degree of immune suppression
Asplenia	LAIV	Pneumococcal Meningococcal Hib[d],[n]	All routine vaccines likely effective
Chronic renal disease	None	Pneumococcal HepB[o]	All routine vaccines likely effective

Abbreviations: AIDS = acquired immunodeficiency syndrome; BCG = bacille Calmette-Guérin; HepB = hepatitis B; Hib = *Haemophilus influenzae* type b; HIV = human immunodeficiency virus; IG = immunoglobulin; IGIV = immune globulin intravenous; IgA = immune globulin A; IgG = immune globulin G; LAIV = live, attenuated influenza vaccine; MMR = measles, mumps, and rubella; MMRV = measles, mumps, rubella, and varicella; OPV = oral poliovirus vaccine (live); PPSV23= pneumococcal polysaccharide vaccine; SCID = severe combined immunodeficiency; Ty21a = live oral typhoid vaccine.

[a] Other vaccines that are universally or routinely recommended should be given if not contraindicated. An exception is patients with B-cell deficiencies receiving immunoglobulins, who should not receive either live or inactivated vaccines, due to safety (live vaccines) and efficacy (live and inactivated vaccines) concerns.

[b] OPV is no longer available in the United States.

[c] This table refers to contraindications for nonemergency vaccination (i.e., the ACIP recommendations); emergency response recommendations are addressed in the clinical guidance for smallpox vaccine use in an emergency.

[d] Children 12-59 months: if unimmunized or received zero or only 1 dose, and that dose was administered before 12 months of age, should receive 2 Hib doses, 8 weeks apart; if received 2 or more doses before age 12 months, and none after 12 months, should receive 1 Hib dose 8 weeks after the last dose; if completed a primary series and received a booster dose at age 12 months or older, no additional Hib doses are recommended.

[e] There are no data to support IgA deficiency as a contraindication for yellow fever vaccine.

[f] Live bacterial vaccines: BCG and oral Ty21a Salmonella Typhi vaccine.

[g] Live viral vaccines: MMR, MMRV, OPV, LAIV, yellow fever, rotavirus, varicella, and vaccinia (smallpox). Nonemergency smallpox vaccination is not recommended for children younger than 18 years or the general public.

[h] Regarding T-lymphocyte immunodeficiency as a contraindication for rotavirus vaccine, data exist only for SCID.

[i] Symptomatic HIV infection or CD4+ T-lymphocyte count of <200/mm^3 or <15% of total lymphocytes for children aged <6 years is a contraindication to yellow fever vaccine administration. Asymptomatic HIV infection with CD4+ T-lymphocyte count of 200-499/mm^3 for persons aged ≥6 years or 15%-24% of total lymphocytes for children aged <6 years is a precaution for yellow fever vaccine administration. Details of yellow fever vaccine recommendations are available from CDC.

[j] Patients 5-18 years of age who have not received a Hib primary series and a booster dose or at least one Hib dose after 14 months of age.

[k] HIV-infected children should be considered for varicella vaccine if CD4+ T-lymphocyte count is ≥15% and should receive MMR vaccine if they are aged ≥12 months and do not have 1) evidence of current severe immunosuppression (i.e., individuals aged ≤5 years must have CD4+T lymphocyte [CD4] percentages ≥15% for ≥6 months; and individuals aged >5 years must have CD4+percentages ≥15% and CD4+≥200 lymphocytes/mm^3 for ≥6 months) and 2) other current evidence of measles, rubella, and mumps immunity. In cases when only CD4+cell counts or only CD4+percentages are available for those older than age 5 years, the assessment of severe immunosuppression can be based on the CD4+values (count or percentage) that are available. In cases when CD4+percentages are not available for those aged ≤5 years, the assessment of severe immunosuppression can be based on age-specific CD4+counts at the time CD4+counts were measured; i.e., absence of severe immunosuppression is defined as ≥6 months above age-specific CD4+count criteria: CD4+count >750 lymphocytes/mm^3 while aged ≤12 months and CD4+count ≥500 lymphocytes/mm^3 while aged 1 through 5 years. See McLean HQ, Fiebelkorn AP, Temte JL, Wallace GS. Prevention of measles, rubella, congenital rubella syndrome, and mumps, 2013: summary recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2013;62(RR-4):1-34.

[l] Withholding inactivated vaccines also is recommended with some forms of immunosuppressive therapy, like anti-CD20 antibodies, induction or consolidation chemotherapy, or patients with major antibody deficiencies receiving immunoglobulins. Inactivated influenza vaccine is an exception, but consideration should be given to repeating doses of any inactivated vaccine administered during these therapies.

[m] Persons younger than 60 months undergoing chemotherapy or radiation therapy who have not received a Hib primary series and a booster dose or at least one Hib dose after 14 months of age; HCT patients of any ages, regardless of Hib vaccine history.

[n] Persons older than 59 months who are asplenic and persons 15 months or older who are undergoing elective splenectomy who have not received a Hib primary series and a booster dose or at least one Hib dose after 14 months of age.

[o] Indicated based on the risk from dialysis-based bloodborne transmission.

Adapted from Table 8-1, ACIP General Best Practice Guidelines for Immunization. January 2021

Appendix A

Contraindications and Precautions[a] to Commonly Used Vaccines

Vaccine	Contraindications	Precautions
DT, Td	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component	GBS <6 weeks after previous dose of tetanus-toxoid–containing vaccine History of Arthus-type hypersensitivity reactions after a previous dose of diphtheria-toxoid-containing or tetanus-toxoid–containing vaccine; defer vaccination until at least 10 years have elapsed since the last tetanus-toxoid-containing vaccine Moderate or severe acute illness with or without fever
DTaP	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component Encephalopathy (e.g., coma, decreased level of consciousness, prolonged seizures), not attributable to another identifiable cause, within 7 days of administration of previous dose of DTP or DTaP	Progressive neurologic disorder, including infantile spasms, uncontrolled epilepsy, progressive encephalopathy; defer DTaP until neurologic status clarified and stabilized GBS <6 weeks after previous dose of tetanus-toxoid–containing vaccine History of Arthus-type hypersensitivity reactions after a previous dose of diphtheria-toxoid–containing or tetanus-toxoid–containing vaccine; defer vaccination until at least 10 years have elapsed since the last tetanus-toxoid–containing vaccine Moderate or severe acute illnes with or without fever
Hepatitis A	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component	Moderate or severe acute illness with or without fever
Hepatitis B	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component Hypersensitivity to yeast	Moderate or severe acute illness with or without fever
Hib	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component Age <6 weeks	Moderate or severe acute illness with or without fever
HPV[b]	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component, including yeast	Moderate or severe acute illness with or without fever
IIV	Severe allergic reaction (e.g., anaphylaxis) after previous dose of influenza vaccine or to vaccine component.	GBS <6 weeks after a previous dose of influenza vaccine Moderate or severe acute illness with or without fever Egg allergy other than hives (e.g., angioedema, respiratory distress, lightheadedness, recurrent emesis; or required epinephrine or another emergency medical intervention). If a vaccine other than RIV or ccIIV is used, the selected vaccine should be administered in an inpatient or outpatient medical setting (including but not necessarily limited to hospitals, clinics, health departments, and physician offices). Vaccine administration should be supervised by a health care provider who is able to recognize and manage severe allergic reactions.

Vaccine	Contraindications	Precautions
IPV	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component	Pregnancy Moderate or severe acute illness with or without fever
LAIV[c]	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component Concomitant use of aspirin or aspirin-containing medication in children and adolescents LAIV4 should not be administered to persons who have taken oseltamivir or zanamivir within the previous 48 hours, peramivir within the previous 5 days, or baloxavir within the previous 17 days.[e] Pregnancy Children aged 2 through 4 years who have received a diagnosis of asthma or whose parents or caregivers report that a health care provider has told them during the preceding 12 months that their child had wheezing or asthma or whose medical record indicates a wheezing episode has occurred during the preceding 12 months. Persons with active cerebrospinal fluid/oropharyngeal communications/leaks. Close contacts and caregivers of severely immunosuppressed persons who require a protected environment. Persons with cochlear implants (due to the potential for CSF leak, which might exist for some period of time after implantation. Providers might consider consultation with a specialist concerning risk of persistent CSF leak if an age-appropriate inactivated or recombinant vaccine cannot be used). Altered Immunocompetence Anatomic or functional asplenia (e.g. sickle cell disease)	GBS <6 weeks after a previous dose of influenza vaccine Asthma in persons aged 5 years old or older Medical conditions which might predispose to higher risk of complications attributable to influenza[d] Moderate or severe acute illness with or without fever
MenACWY	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component, including yeast	Moderate or severe acute illness with or without fever Preterm birth (MenACWY-CRM)[f]
MenB	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component	Moderate or severe acute illness with or without fever Pregnancy Latex sensitivity (MenB-4C)

Vaccine	Contraindications	Precautions
MMR[g],[h]	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component Pregnancy Known severe immunodeficiency (e.g., from hematologic and solid tumors, receipt of chemotherapy, congenital immunodeficiency, long-term immunosuppressive therapy[i] or patients with HIV infection who are severely immunocompromised) Family history of altered immunocompetence[j]	Recent (≤11 months) receipt of antibody-containing blood product (specific interval depends on product) History of thrombocytopenia or thrombocytopenic purpura Need for tuberculin skin testing or interferon-gamma release assay (IGRA) testing[k] Moderate or severe acute illness with or without fever
MPSV4	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component	Moderate or severe acute illness with or without fever
PCV13	Severe allergic reaction (e.g., anaphylaxis) after a previous dose of PCV13 or any diphtheria-toxoid–containing vaccine or to a component of a vaccine (PCV13 or any diphtheria-toxoid–containing vaccine), including yeast	Moderate or severe acute illness with or without fever
PPSV23	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component	Moderate or severe acute illness with or without fever
RIV	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component	GBS <6 weeks after a previous dose of influenza vaccine Moderate or severe acute illness with or without fever
Rotavirus	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component SCID History of intussusception	Altered immunocompetence other than SCID Chronic gastrointestinal disease[l] Spina bifida or bladder exstrophy[l] Moderate or severe acute illness with or without fever
Tdap	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component Encephalopathy (e.g., coma, decreased level of consciousness, prolonged seizures), not attributable to another identifiable cause, within 7 days of administration of previous dose of DTP, DTaP, or Tdap	GBS <6 weeks after a previous dose of tetanus-toxoid–containing vaccine Progressive or unstable neurological disorder, uncontrolled seizures, or progressive encephalopathy until a treatment regimen has been established and the condition has stabilized History of Arthus-type hypersensitivity reactions after a previous dose of diphtheria-toxoid—containing or tetanus-toxoid–containing vaccine; defer vaccination until at least 10 years have elapsed since the last tetanus-toxoid–containing vaccine Moderate or severe acute illness with or without fever

Vaccine	Contraindications	Precautions
Varicella[g],[h]	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component Known severe immunodeficiency (e.g., from hematologic and solid tumors, receipt of chemotherapy, congenital immunodeficiency, long-term immunosuppressive therapy[i] or patients with HIV infection who are severely immunocompromised)[g] Pregnancy Family history of altered immunocompetence[j]	Recent (≤11 months) receipt of antibody-containing blood product (specific interval depends on product) Moderate or severe acute illness with or without fever Use of aspirin or aspirin-containing products[m] Receipt of specific antiviral drugs (acyclovir, famciclovir, or valacyclovir) 24 hours before vaccination (avoid use of these antiviral drugs for 14 days after vaccination)
Zoster	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component	Moderate or severe acute illness with or without fever

Abbreviations: DT = diphtheria and tetanus toxoids; DTaP = diphtheria and tetanus toxoids and acellular pertussis; DTP = diphtheria toxoid, tetanus toxoid, and pertussis; GBS = Guillain-Barré syndrome; Hib = *Haemophilus influenzae* type b; HIV = human immunodeficiency virus; HPV = human papillomavirus; IIV = inactivated influenza vaccine; IPV = inactivated poliovirus; LAIV = live, attenuated influenza vaccine; MenACWY = quadrivalent meningococcal conjugate vaccine; MMR = measles, mumps, and rubella; MPSV4 = quadrivalent meningococcal polysaccharide vaccine; PCV13 = pneumococcal conjugate vaccine; PPSV23= pneumococcal polysaccharide vaccine; SCID = severe combined immunodeficiency; RIV=recombinant influenza vaccine; Td = tetanus and diphtheria toxoids; Tdap = tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis.

[a] Events or conditions listed as precautions should be reviewed carefully. Benefits of and risks for administering a specific vaccine to a person under these circumstances should be considered. If the risk from the vaccine is believed to outweigh the benefit, the vaccine should not be administered. If the benefit of vaccination is believed to outweigh the risk, the vaccine should be administered. Whether and when to administer DTaP to children with proven or suspected underlying neurologic disorders should be decided on a case-by-case basis.

[b] HPV vaccine is not recommended during pregnancy.

[c] In addition, ACIP recommends LAIV not be used for pregnant women, immunosuppressed persons, and children aged 2-4 years who have asthma or who have had a wheezing episode noted in the medical record within the past 12 months, or for whom parents report that a health-care provider stated that they had wheezing or asthma within the last 12 months. LAIV should not be administered to persons who received influenza antiviral medications oseltamivir or zanamivir within the previous 48 hours, peramivir within the previous 5 days, or baloxavir within the previous 17 days. Persons who care for severely immunosuppressed persons who require a protective environment should not receive LAIV, or should avoid contact with such persons for 7 days after receipt.

[d] See reference: See reference: Grohskopf L, Alyanak E, Broder KR, et al., Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2020–21 Influenza Season. MMWR Recomm Rep. 2020;69(No. RR-8):1-26.

[e] These values are based on the clearance of the particular antiviral. LAIV4 should not be administered to persons who have taken oseltamivir or zanamivir within the previous 48 hours, peramivir within the previous 5 days, or baloxavir within the previous 17 days. This "contraindication" is due to concern with reduced effectiveness of the vaccine. To obtain specific information, please refer to Grohskopf LA, Alyanak, E, Broder KR, et. al. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2020–21 Influenza Season. MMWR Recomm Rep 2020;69(No. RR-8:1-26. Also at https://www.cdc.gov/mmwr/volumes/69/rr/pdfs/rr6908a1-H.pdf.

[f] This precaution applies to infants younger than 9 months old.

[g] HIV-infected children may receive varicella vaccine if CD4+ T-lymphocyte count is ≥15% and should receive MMR vaccine if they are aged ≥12 months and do not have evidence of current severe immunosuppression (i.e., individuals aged ≤5 years must have CD4+T lymphocyte [CD4] percentages ≥15% for ≥6 months; and individuals aged >5 years must have CD4+percentages ≥15% and CD4+≥200 lymphocytes/mm^3 for ≥6 months) or other current evidence of measles, rubella, and mumps immunity. In cases when only CD4+cell counts or only CD4+percentages are available for those older than age 5 years, the assessment of severe immunosuppression can be based on the CD4+values (count or percentage) that are available. In cases when CD4+percentages are not available for those aged ≤5 years, the assessment of severe immunosuppression can be based on age-specific CD4+counts at the time CD4+counts were measured; i.e., absence of severe immunosuppression is defined as ≥6 months above age-specific CD4+count criteria: CD4+count >750 lymphocytes/mm^3 while aged ≤12 months and CD4+count ≥500 lymphocytes/mm^3 while aged 1 through 5 years. Sources: 1) McLean HQ, Fiebelkorn AP, Temte JL, Wallace GS. Prevention of measles, rubella, congenital rubella syndrome, and mumps, 2013: summary recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2013;62(RR-4):1-34. 2) CDC. Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 1997;46(RR-8):1-24.

[h] MMR and varicella-containing vaccines can be administered on the same day. If not administered on the same day, these vaccines should be separated by at least 28 days.

[i] A substantially immunosuppressive steroid dose is considered to be ≥2 weeks of daily receipt of 20 mg or 2 mg/kg body weight of prednisone or equivalent.

[j] Family history of congenital or hereditary immunodeficiency in first-degree relatives (e.g., parents and siblings), unless the immune competence of the potential vaccine recipient has been substantiated clinically or verified by a laboratory.

[k] If active tuberculosis is suspected, MMR should be delayed. Measles vaccination might suppress tuberculin reactivity temporarily. Measles-containing vaccine can be administered on the same day as tuberculin skin or IGRA testing. If testing cannot be performed until after the day of MMR vaccination, the test should be postponed for ≥4 weeks after the vaccination. If an urgent need exists to skin test or IGRA, do so with the understanding that reactivity might be reduced by the vaccine.

[l] For RV1 only, based on latex in product/packaging. Note that anaphylactic allergy to latex is covered in the contraindication, and would also be isolated to RV 1 in the case of latex. For more details see Cortese MM, Parashar UD. Prevention of rotavirus gastroenteritis among infants and children: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2009;58(RR-2):1-25.

[m] No adverse events associated with the use of aspirin or aspirin-containing products after varicella vaccination have been reported; however, the vaccine manufacturer recommends that vaccine recipients avoid using aspirin or aspirin-containing products for 6 weeks after receiving varicella vaccines because of the association between aspirin use and Reye syndrome after varicella. Vaccination with subsequent close monitoring should be considered for children who have rheumatoid arthritis or other conditions requiring therapeutic aspirin. The risk for serious complications associated with aspirin is likely to be greater in children in whom natural varicella develops than it is in children who receive the vaccine containing attenuated VZV. No association has been documented between Reye syndrome and analgesics or antipyretics that do not contain aspirin.

Adapted from Table 4-1, ACIP General Best Practice Guidelines for Immunization. January 2021

Appendix A

Additional Resources for Schedules and Recommendations

Immunization Schedules

- Recommended Immunization Schedules for Persons Aged 0 Through 18 Years: https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html
- Catch-up Schedule for Persons Aged 0 Through 18 Years: https://www.cdc.gov/vaccines/schedules/hcp/imz/catchup.html
- Recommended Immunization Schedules for Persons Aged 19 Years or Older: https://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html
- Schedules Changes & Guidance: https://www.cdc.gov/vaccines/schedules/hcp/schedule-changes.html
- Summary of Recommendations for Child/Teen Immunization (Immunization Action Coalition): http://www.immunize.org/catg.d/p2010.pdf
- Summary of Recommendations for Adult Immunization (Immunization Action Coalition): http://www.immunize.org/catg.d/p2011.pdf
- More Schedule-Related Resources (e.g. schedule presentation graphics, prior immunization schedules): https://www.cdc.gov/vaccines/schedules/hcp/schedule-related-resources.html

Recommendations

- Vaccine-specific ACIP Recommendations and Guidelines: https://www.cdc.gov/vaccines/hcp/acip-recs/index.html
- Vaccines by Disease: https://www.cdc.gov/vaccines/vpd/vaccines-diseases.html
- Adults with Health Conditions: https://www.cdc.gov/vaccines/adults/rec-vac/health-conditions/index.html
- Guide to Contraindications and Precautions to Commonly Used Vaccines (Immunization Action Coalition): http://www.immunize.org/catg.d/p3072a.pdf
- Guide to Contraindications and Precautions to Commonly Used Vaccines in Adults (Immunization Action Coalition): http://www.immunize.org/catg.d/p3072.pdf
- Recommended Vaccines for Healthcare Workers: https://www.cdc.gov/vaccines/adults/rec-vac/hcw.html
- Travel Vaccines: https://wwwnc.cdc.gov/travel/page/travel-vaccines
- Vaccines for Immigrants and Refugees: https://www.cdc.gov/vaccines/adults/rec-vac/immigrants-refugees.html

Appendix B: Vaccines

Appendix B

United States Vaccine Names

United States Vaccines

Vaccine	Trade Name	Abbreviation	Manufacturer	Route	Doses in Routine Series	Approved Ages	Comments
Adenovirus	Adenovirus Type 4 & Type 7	N/A	Teva Pharmaceutical Industries Ltd.	Oral (2 Tablets)	1	17-50 years	Live: Approved for military populations; not approved for pregnant women
Anthrax	BioThrax®	AVA	Emergent BioSolutions	IM	3	18-65 years	Cell-free filtrate from avirulent strain, Adj.
Cholera	Vaxchora™†	N/A	Emergent BioSolutions	Oral (Liquid)	1	18-64 years	Live Attenuated
DTaP	Daptacel®	DTaP	Sanofi	IM	5	6 weeks-6 years	Inactivated, Adj.
	Infanrix™	DTaP	GlaxoSmithKline	IM	5	6 weeks-6 years	Inactivated, Adj.
DT	N/A (Generic)	DT	Sanofi	IM	5	6 weeks-6 years	Inactivated, Adj.: Use when pertussis is contraindicated
***Haemophilus influenzae type b* (Hib)**	ActHIB®	Hib (PRP-T)	Sanofi	IM	4	2 months-5 years	Inactivated (Tetanus toxoid conjugate)
	Hiberix™	Hib (PRP-T)	GlaxoSmithKline	IM	4	6 weeks- 4 years	Inactivated (Tetanus toxoid conjugate)
	PedvaxHIB®	Hib (PRP-OMP)	Merck	IM	3	2-71 months	Inactivated, Adj. (Meningococcal conjugate)
Hepatitis A	Havrix™	HepA	GlaxoSmithKline	IM	2	Pediatric: 12 months-18 years; Adult: ≥19 years	Inactivated, Adj.
	Vaqta®	HepA	Merck	IM	2	Pediatric: 12 months-18 years; Adult: ≥19 years	Inactivated, Adj.
Hepatitis B	Engerix-B™	HepB	GlaxoSmithKline	IM	3	Pediatric: Birth-19 years Adult: ≥20 years	Recombinant, Adj.
	Recombivax HB®	HepB	Merck	IM	3	Pediatric: Birth-19 years Adult: ≥20 years	Recombinant, Adj.
	Heplisav-B®	HepB	Dynavax Technologies	IM	2	≥18 years	Recombinant, Adj.
Herpes Zoster (Shingles)	Shingrix™	RZV	GlaxoSmithKline	IM	2	≥50 years	Recombinant, Adj.

Vaccine	Trade Name	Abbreviation	Manufacturer	Route	Doses in Routine Series	Approved Ages	Comments
Human Papillomavirus (HPV)	Gardasil® 9	9vHPV	Merck	IM	2 or 3	9-45 years	Recombinant, Adj. ACIP recommends 9-26 years
Influenza*	Afluria Quadrivalent®	IIV4	Seqirus	IM	1 or 2	≥6 months	Inactivated
	Fluad®	IIV3	Seqirus	IM	1	≥65 years	Inactivated, Adj.
	Fluad® Quadrivalent	IIV4	Seqirus	IM	1	≥65 years	Inactivated, Adj.
	Fluarix™ Quadrivalent	IIV4	GlaxoSmithKline	IM	1 or 2	≥6 months	Inactivated
	Flublok® Quadrivalent	RIV4	Sanofi	IM	1	≥18 years	Recombinant, Egg-Free
	Flucelvax® Quadrivalent	ccIIV4	Seqirus	IM	1 or 2	≥4 years	Cell-culture, Egg-free
	FluLaval™ Quadrivalent	IIV4	GlaxoSmithKline	IM	1 or 2	≥6 months	Inactivated
	FluMist® Quadrivalent	LAIV4	AstraZeneca	Intranasal	1 or 2	2-49 years	Live Attenuated
	Fluzone® Quadrivalent	IIV4	Sanofi	IM	1 or 2	≥6 months	Inactivated
	Fluzone® High-Dose Quadrivalent	HD-IIV4	Sanofi	IM	1	≥65 years	Inactivated
Japanese encephalitis	Ixiaro®	JE	Valneva	IM	2	≥2 months	Inactivated, Adj.
Measles, Mumps, Rubella	M-M-R® II	MMR	Merck	SC	2	≥12 months	Live Attenuated
Meningococcal (serogroups A, C, W, and Y)	Menactra®	MenACWY-D	Sanofi	IM	2	9 months-55 years	Inactivated (Polysaccharide diphtheria toxoid conjugate)
	Menquadfi™	MenACWY-TT	Sanofi	IM	2	≥2 years	Inactivated (Polysaccharide tetanus toxoid conjugate)
	Menveo™	MenACWY-CRM	GlaxoSmithKline	IM	2	2 months-55 years	Inactivated (Polysaccharide CRM_{197} conjugate)
Meningococcal (serogroup B)	Trumenba®	MenB-FHbp	Pfizer	IM	2 or 3	10-25 years	Recombinant, Adj.
	Bexsero™	MenB-4C	GlaxoSmithKline	IM	2	10-25 years	Recombinant, Adj.

Vaccine	Trade Name	Abbreviation	Manufacturer	Route	Doses in Routine Series	Approved Ages	Comments
Pneumococcal	Pneumovax® 23	PPSV23	Merck	IM or SC	1	≥2 years	Inactivated Polysaccharide
	Prevnar 13®	PCV13	Pfizer	IM	4 (pediatric) 1 (adult)	Pediatric: ≥6 weeks Adult: >65 years	Inactivated, Adj. (CRM_{197} conjugate)
Polio	Ipol®	IPV	Sanofi	IM or SC	4	≥6 weeks	Inactivated
Rabies	Imovax®	N/A	Sanofi	IM	2-3 (pre-exposure) 4 (post-exposure)	All ages	Inactivated
	RabAvert®	N/A	Bavarian Nordic	IM	2-3 (pre-exposure) 4 (post-exposure)	All ages	Inactivated
Rotavirus	RotaTeq®	RV5	Merck	Oral (Liquid)	3	6-32 weeks	Live, Pentavalent
	Rotarix™	RV1	GlaxoSmithKline	Oral (Liquid)	2	6-24 weeks	Live, Monovalent
Tetanus, (reduced) Diphtheria	Tenivac®	Td	Sanofi	IM	1 (Every 10 years)	≥7 years	Inactivated, Adj.
	TdVax™	Td	Massachusetts Biological Labs	IM	1 (Every 10 years)	≥7 years	Inactivated, Adj.
Tetanus, (reduced) Diphtheria, (reduced) Pertussis	Boostrix™	Tdap	GlaxoSmithKline	IM	1	≥10 years	Inactivated, Adj.
	Adacel®	Tdap	Sanofi	IM	1	10-64 years	Inactivated, Adj.
Typhoid	Typhim Vi®	N/A	Sanofi	IM	1	≥2 years	Inactivated Polysaccharide
	Vivotif®	N/A	Emergent BioSolutions	Oral (Capsules)	4	≥6 years	Live Attenuated
Varicella	Varivax®	VAR	Merck	SC	2	≥12 months	Live Attenuated
Smallpox (Vaccinia)	ACAM2000®	—	Emergent BioSolutions	Percutaneous	1	All ages	Live Attenuated
Smallpox and Monkeypox	JYNNEOS®	—	Bavarian Nordic	SC	2	≥18 years	Live, Non-replicating
Yellow Fever	YF-Vax®	YF	Sanofi	SC	1	≥9 months	Live Attenuated

The abbreviations on this table (Column 3) were standardized jointly by staff of the Centers for Disease Control and Prevention, Advisory Committee on Immunization Practices (ACIP) Work Groups, the editor of the Morbidity and Mortality Weekly Report (MMWR), the editor of Epidemiology and Prevention of Vaccine-Preventable Diseases (the Pink Book), ACIP members, and liaison organizations to the ACIP. These abbreviations are intended to provide a uniform approach to vaccine references used in ACIP Recommendations and Policy Notes published in the MMWR, the Pink Book, and the American Academy of Pediatrics Red Book, and in the U.S. immunization schedules for children, adolescents, and adults. In descriptions of combination vaccines, a hyphen (-) indicates products in which the active components are supplied in their final (combined) form by the manufacturer; a slash (/) indicates products in which active components must be mixed by the user.

"Doses in a Routine Series" (Column 6) reflects doses administered to a healthy patient at the recommended ages. It does not necessarily reflect schedules for patients with health conditions or other high-risk factors, alternative schedules, catch-up schedules, or booster doses not part of an initial series. For some combination vaccines, this column represents the routine number of doses for that product, and not necessarily the total number of doses in a complete series for the components. (For example, Kinrix or Quadracel may be used for only 1 dose of multi-dose DTaP and IPV series.)

"Adj." in the "Comments" column indicates that the vaccine contains an adjuvant.

A hyphen in an age range means "through" (i.e., "6 weeks-6 years" means 6 weeks through 6 years [to the 7th birthday]).

*All influenza vaccines in this table are 2020-2021 northern hemisphere formulations. For the most current recommendations on influenza, see: https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/flu.html

†May be limited in supply as manufacturer has temporarily stopped production

United States Combination Vaccines

Vaccine	Trade Name	Abbreviation	Manufacturer	Route	Doses in Routine Series	Approved Ages	Comments
DTaP, Polio	Kinrix™	DTaP-IPV	GlaxoSmithKline	IM	1	4-6 years	Inactivated, Adj.: Approved as 5th DTaP and 4th IPV.
	Quadracel®	DTaP-IPV	Sanofi	IM	1	4-6 years	Inactivated, Adj.: Approved as 5th DTaP and 4th IPV.
DTaP, hepatitis B, Polio	Pediarix™	DTaP-HepB-IPV	GlaxoSmithKline	IM	3	6 weeks-6 years	Inactivated, Adj.: Approved for 2, 4, 6 month doses.
DTaP, Polio, *Haemophilus* influenzae type b	Pentacel®	DTaP-IPV/Hib	Sanofi	IM	4	6 weeks-4 years	4 Inactivated, Adj.: Approved for 2, 4, 6, 15-18 month doses.
DTaP, Polio, *Haemophilus influenzae* type b, hepatitis B	Vaxelis™	DTaP-IPV-Hib-HepB	Sanofi	IM	3	6 weeks-4 years	Inactivated, Adj.: Approved for 2, 4, 6 month doses.
Hepatitis A, Hepatitis B	Twinrix™	HepA-HepB	GlaxoSmithKline	IM	3	≥18 years	Inactivated/Recombinant, Adj. Pediatric HepA + Adult HepB
Measles, Mumps, Rubella, Varicella	ProQuad®	MMRV	Merck	SC	2	12 months-12 years	Live Attenuated

The abbreviations on this table (Column 3) were standardized jointly by staff of the Centers for Disease Control and Prevention, Advisory Committee on Immunization Practices (ACIP) Work Groups, the editor of the Morbidity and Mortality Weekly Report (MMWR), the editor of Epidemiology and Prevention of Vaccine-Preventable Diseases (the Pink Book), ACIP members, and liaison organizations to the ACIP. These abbreviations are intended to provide a uniform approach to vaccine references used in ACIP Recommendations and Policy Notes published in the MMWR, the Pink Book, and the American Academy of Pediatrics Red Book, and in the U.S. immunization schedules for children, adolescents, and adults. In descriptions of combination vaccines, a hyphen (-) indicates products in which the active components are supplied in their final (combined) form by the manufacturer; a slash (/) indicates products in which active components must be mixed by the user.

"Doses in a Routine Series" (Column 6) reflects doses administered to a healthy patient at the recommended ages. It does not necessarily reflect schedules for patients with health conditions or other high-risk factors, alternative schedules, catch-up schedules, or booster doses not part of an initial series. For some combination vaccines, this column represents the routine number of doses for that product, and not necessarily the total number of doses in a complete series for the components. (For example, Kinrix or Quadracel may be used for only 1 dose of multi-dose DTaP and IPV series.)

"Adj." in the "Comments" column indicates that the vaccine contains an adjuvant.

A hyphen in an age range means "through" (i.e., "6 weeks-6 years" means 6 weeks through 6 years [to the 7th birthday]).

February 2021

Vaccine Excipient Summary

Excipients Included in U.S. Vaccines, by Vaccine

In addition to weakened or killed disease antigens (such as weakened, killed, or parts of viruses or bacteria), vaccines contain very small amounts of other ingredients – excipients.

Some excipients are added to a vaccine for a specific purpose. These include:

- **Preservatives**, to prevent contamination. For example, thimerosal.
- **Adjuvants**, to help stimulate a stronger immune response. For example, aluminum salts.
- **Stabilizers**, to keep the vaccine potent during transportation and storage. For example, sugars or gelatin.

Others are residual trace amounts of materials that were used during the manufacturing process and removed. These can include:

- **Cell culture materials**, used to grow the vaccine antigens. For example, egg protein, various culture media.
- **Inactivating ingredients**, used to kill viruses or inactivate toxins. For example, formaldehyde.
- **Antibiotics**, used to prevent contamination by bacteria. For example, neomycin.

The following table lists substances, other than active ingredients (i.e., antigens), shown in the manufacturers' package insert (PI) as being contained in the final formulation of each vaccine. **Substances used in the manufacture of a vaccine but not listed as contained in the final product (e.g., culture media) can be found in each PI, but are not shown on this table.** Each PI, which can be found on the FDA's website (see below) contains a description of that vaccine's manufacturing process, including the amount and purpose of each substance. In most PIs, this information is found in Section 11: "Description." Please refer to the PI for a complete list of ingredients or excipients. A table listing vaccine excipients and media by excipient is published by the Institute for Vaccine Safety at Johns Hopkins University, and can be found at http://www.vaccinesafety.edu/components-Excipients.htm.

Vaccine Excipient Table

Vaccine (Trade Name)	Package Insert Date	Contains[a]
Adenovirus	10/2019	monosodium glutamate, sucrose, D-mannose, D-fructose, dextrose, human serum albumin, potassium phosphate, plasdone C, anhydrous lactose, microcrystalline cellulose, polacrilin potassium, magnesium stearate, cellulose acetate phthalate, alcohol, acetone, castor oil, FD&C Yellow #6 aluminum lake dye
Anthrax (Biothrax)	11/2015	aluminum hydroxide, sodium chloride, benzethonium chloride, formaldehyde
BCG (Tice)	02/2009	glycerin, asparagine, citric acid, potassium phosphate, magnesium sulfate, iron ammonium citrate, lactose
Cholera (Vaxchora)	06/2016	ascorbic acid, hydrolyzed casein, sodium chloride, sucrose, dried lactose, sodium bicarbonate, sodium carbonate
Dengue (Dengvaxia)	06/2019	sodium chloride, essential amino acids (including L-phenylalanine), non-essential amino acids, L-arginine hydrochloride, sucrose, D-trehalose dihydrate, D-sorbitol, trometamol, urea
DT (Sanofi)	06/2018	aluminum phosphate, isotonic sodium chloride, formaldehyde
DTaP (Daptacel)	01/2021[b]	aluminum phosphate, formaldehyde, glutaraldehyde, 2-phenoxyethanol
DTaP (Infanrix)	01/2021[b]	formaldehyde, aluminum hydroxide, sodium chloride, polysorbate 80 (Tween 80)
DTaP-IPV (Kinrix)	01/2021[b]	formaldehyde, aluminum hydroxide, sodium chloride, polysorbate 80 (Tween 80), neomycin sulfate, polymyxin B
DTaP-IPV (Quadracel)	02/2021	formaldehyde, aluminum phosphate, 2-phenoxyethanol, polysorbate 80, glutaraldehyde, neomycin, polymyxin B sulfate, bovine serum albumin
DTaP-HepB-IPV (Pediarix)	01/2021[b]	formaldehyde, aluminum hydroxide, aluminum phosphate, sodium chloride, polysorbate 80 (Tween 80), neomycin sulfate, polymyxin B, yeast protein
DTaP-IPV/Hib (Pentacel)	12/2019	aluminum phosphate, polysorbate 80, sucrose, formaldehyde, glutaraldehyde, bovine serum albumin, 2-phenoxyethanol, neomycin, polymyxin B sulfate
DTaP-IPV-Hib-HepB (Vaxelis)	10/2020	polysorbate 80, formaldehyde, glutaraldehyde, bovine serum albumin, neomycin, streptomycin sulfate, polymyxin B sulfate, ammonium thiocyanate, yeast protein, aluminum
Ebola Zaire (ERVEBO)	01/2021[b]	Tromethamine, rice-derived recombinant human serum albumin, host cell DNA, benzonase, rice protein
Hib (ActHIB)	05/2019	sodium chloride, formaldehyde, sucrose
Hib (Hiberix)	04/2018	formaldehyde, sodium chloride, lactose
Hib (PedvaxHIB)	01/2021[b]	amorphous aluminum hydroxyphosphate sulfate, sodium chloride
Hep A (Havrix)	01/2021[b]	MRC-5 cellular proteins, formalin, aluminum hydroxide, amino acid supplement, phosphate-buffered saline solution, polysorbate 20, neomycin sulfate, aminoglycoside antibiotic
Hep A (Vaqta)	01/2021[b]	amorphous aluminum hydroxyphosphate sulfate, non-viral protein, DNA, bovine albumin, formaldehyde, neomycin, sodium borate, sodium chloride, other process chemical residuals
Hep B (Engerix-B)	01/2021[b]	aluminum hydroxide, yeast protein, sodium chloride, disodium phosphate dihydrate, sodium dihydrogen phosphate dihydrate
Hep B (Recombivax)	12/2018	formaldehyde, potassium aluminum sulfate, amorphous aluminum hydroxyphosphate sulfate, yeast protein
Hep B (Heplisav-B)	05/2020	yeast protein, yeast DNA, deoxycholate, phosphorothioate linked oligodeoxynucleotide, sodium phosphate, dibasic dodecahydrate, sodium chloride, monobasic dehydrate, polysorbate 80
Hep A/Hep B (Twinrix)	01/2021[b]	MRC-5 cellular proteins, formalin, aluminum phosphate, aluminum hydroxide, amino acids, sodium chloride, phosphate buffer, polysorbate 20, neomycin sulfate, yeast protein
HPV (Gardasil 9)	08/2020	amorphous aluminum hydroxyphosphate sulfate, sodium chloride, L-histidine, polysorbate 80, sodium borate, yeast protein

Vaccine (Trade Name)	Package Insert Date	Contains[a]
Influenza (Afluria) Quadrivalent[c]	07/2020	sodium chloride, monobasic sodium phosphate, dibasic sodium phosphate, monobasic potassium phosphate, potassium chloride, calcium chloride, sodium taurodeoxycholate, ovalbumin, sucrose, neomycin sulfate, polymyxin B, beta-propiolactone, hydrocortisone, thimerosal (multi-dose vials)
Influenza (Fluad)[c]	10/2020	squalene, polysorbate 80, sorbitan trioleate, sodium citrate dehydrate, citric acid monohydrate, neomycin, kanamycin, hydrocortisone, egg proteins, cetyltrimethylammonium bromide (CTAB), formaldehyde
Influenza (Fluad) Quadrivalent[c]	11/2020	squalene, polysorbate 80, sorbitan trioleate, sodium citrate dihydrate, citric acid monohydrate, neomycin, kanamycin, hydrocortisone, egg protein, formaldehyde
Influenza (Fluarix) Quadrivalent[c]	07/2020	octoxynol-10 (TRITON X-100), α-tocopheryl hydrogen succinate, polysorbate 80 (Tween 80), hydrocortisone, gentamicin sulfate, ovalbumin, formaldehyde, sodium deoxycholate, sodium phosphate-buffered isotonic sodium chloride
Influenza (Flublok) Quadrivalent[c]	06/2020	sodium chloride, monobasic sodium phosphate, dibasic sodium phosphate, polysorbate 20 (Tween 20), baculovirus and *Spodoptera frugiperda* cell proteins, baculovirus and cellular DNA, Triton X-100
Influenza (Flucelvax) Quadrivalent[c]	03/2020	Madin Darby Canine Kidney (MDCK) cell protein, phosphate buffered saline, protein other than HA, MDCK cell DNA, polysorbate 80, cetyltrimethlyammonium bromide, and β-propiolactone, thimerosal (multi-dose vials)
Influenza (Flulaval) Quadrivalent[c]	2020	ovalbumin, formaldehyde, sodium deoxycholate, α-tocopheryl hydrogen succinate, polysorbate 80, phosphate-buffered saline solution
Influenza (Fluzone) Quadrivalent[c]	2020	formaldehyde, egg protein, octylphenol ethoxylate (Triton X-100), sodium phosphate-buffered isotonic sodium chloride solution, thimerosal (multi-dose vials)
Influenza (Fluzone) High Dose[c]	2020	egg protein, octylphenol ethoxylate (Triton X-100), sodium phosphate-buffered isotonic sodium chloride solution, formaldehyde
Influenza (FluMist) Quadrivalent[c]	08/2020	monosodium glutamate, hydrolyzed porcine gelatin, arginine, sucrose, dibasic potassium phosphate, monobasic potassium phosphate, ovalbumin, gentamicin sulfate, ethylenediaminetetraacetic acid (EDTA)
IPV (Ipol)	01/2021[b]	calf bovine serum albumin, 2-phenoxyethanol, formaldehyde, neomycin, streptomycin, polymyxin B, M-199 medium
Japanese Encephalitis (Ixiaro)	09/2018	aluminum hydroxide, protamine sulfate, formaldehyde, bovine serum albumin, host cell DNA, sodium metabisulphite, host cell protein
MenACWY (Menactra)	04/2018	sodium phosphate buffered isotonic sodium chloride solution, formaldehyde, diphtheria toxoid protein carrier
MenACWY (MenQuadfi)	01/2021[b]	sodium chloride, sodium acetate, formaldehyde
MenACWY (Menveo)	07/2020	formaldehyde, CRM_{197} protein
MenB (Bexsero)	01/2021[b]	aluminum hydroxide, sodium chloride, histidine, sucrose, kanamycin
MenB (Trumenba)	2018	polysorbate 80, aluminum phosphate, histidine buffered saline
MMR (MMR-II)	12/2020	sorbitol, sucrose, hydrolyzed gelatin, recombinant human albumin, neomycin, fetal bovine serum, WI-38 human diploid lung fibroblasts
MMRV (ProQuad) (Frozen: Recombinant Albumin)	01/2021[b]	MRC-5 cells including DNA and protein, sucrose, hydrolyzed gelatin, sodium chloride, sorbitol, monosodium L-glutamate, sodium phosphate dibasic, recombinant human albumin, sodium bicarbonate, potassium phosphate monobasic, potassium chloride, potassium phosphate dibasic, neomycin, bovine calf serum, other buffer and media ingredients
PCV13 (Prevnar 13)	08/2017	CRM_{197} carrier protein, polysorbate 80, succinate buffer, aluminum phosphate
PPSV-23 (Pneumovax)	09/2020	isotonic saline solution, phenol
Rabies (Imovax)	10/2019	human albumin, neomycin sulfate, phenol red, beta-propiolactone
Rabies (RabAvert)	2018	chicken protein, polygeline (processed bovine gelatin), human serum albumin, potassium glutamate, sodium EDTA, ovalbumin, neomycin, chlortetracycline, amphotericin B
Rotavirus (RotaTeq)	01/2021[b]	sucrose, sodium citrate, sodium phosphate monobasic monohydrate, sodium hydroxide, polysorbate 80, cell culture media, fetal bovine serum

Appendix B

Vaccine (Trade Name)	Package Insert Date	Contains[a]
Rotavirus (Rotarix)	01/2021[b]	dextran, Dulbecco's Modified Eagle Medium (sodium chloride, potassium chloride, magnesium sulfate, ferric (III) nitrate, sodium phosphate, sodium pyruvate, D-glucose, concentrated vitamin solution, L-cystine, L-tyrosine, amino acids, L-glutamine, calcium chloride, sodium hydrogenocarbonate, and phenol red), sorbitol, sucrose, calcium carbonate, sterile water, xanthan [Porcine circovirus type 1 (PCV1) is present in Rotarix. PCV-1 is not known to cause disease in humans.]
Smallpox (Vaccinia) (ACAM2000)	03/2018	HEPES, 2% human serum albumin, 0.5 - 0.7% sodium chloride USP, 5% Mannitol USP, neomycin, polymyxin B, 50% Glycerin USP, 0.25% phenol USP
Td (Tenivac)	11/2019	aluminum phosphate, formaldehyde, sodium chloride
Td (TDVAX)	09/2018	aluminum phosphate, formaldehyde, thimerosal
Tdap (Adacel)	12/2020	aluminum phosphate, formaldehyde, 2-phenoxyethanol, glutaraldehyde
Tdap (Boostrix)	09/2020	formaldehyde, aluminum hydroxide, sodium chloride, polysorbate 80
Typhoid (Typhim Vi)	03/2020	formaldehyde, phenol, polydimethylsiloxane, disodium phosphate, monosodium phosphate, sodium chloride
Typhoid (Vivotif Ty21a)	9/2013	sucrose, ascorbic acid, amino acids, lactose, magnesium stearate, gelatin
Varicella (Varivax) Frozen	01/2021[b]	sucrose, hydrolyzed gelatin, sodium chloride, monosodium L-glutamate, sodium phosphate dibasic, potassium phosphate monobasic, potassium chloride, MRC-5 human diploid cells including DNA & protein, sodium phosphate monobasic, EDTA, neomycin, fetal bovine serum
Yellow Fever (YF-Vax)	2/2019	sorbitol, gelatin, sodium chloride
Zoster (Shingles) (Shingrix)	01/2021[b]	sucrose, sodium chloride, dioleoyl phosphatidylcholine (DOPC), 3-*O*-desacl-4'monophosphoryl lipid A (MPL), QS-21 (a saponin purified from plant extract *Quillaja saponaria* Molina), potassium dihydrogen phosphate, cholesterol, sodium dihydrogen phosphate dihydrate, disodium phosphate anhydrous, dipotassium phosphate, polysorbate 80, host cell protein and DNA

Abbreviations: DT = diphtheria and tetanus toxoids; DTaP = diphtheria and tetanus toxoids and acellular pertussis; Hep A = Hepatitis A; Hep B = Hepatitis B; Hib = *Haemophilus influenzae* type b; HPV = human papillomavirus; IPV = inactivated poliovirus; LAIV = live, attenuated influenza vaccine; MenACWY = quadrivalent meningococcal conjugate vaccine; MenB = serogroup B meningococcal vaccine; MMR = measles, mumps, and rubella; MMRV = measles, mumps, rubella, varicella; PCV13 = pneumococcal conjugate vaccine; PPSV23= pneumococcal polysaccharide vaccine; Td = tetanus and diphtheria toxoids; Tdap = tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis.

[a]All information was extracted from manufacturers' package inserts. The date shown in the Date column of the table is the edition date of the PI in use in January 2021 by month and year. In some cases, only a year was printed on the PI. If in doubt about whether a PI has been updated since this table was prepared, check the FDA's website at:

http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm093833.htm

[b]The PI was not dated and this is the date the PI was reviewed for this table.

[c]All influenza vaccine in this table are 2020-21 northern hemisphere formulation.

January 2021

Latex in Vaccine Packaging

"Immediate-type allergic reactions due to latex allergy have been described after vaccination, but such reactions are rare. If a person reports a severe anaphylactic allergy to latex, vaccines supplied in vials or syringes that contain natural rubber latex should be avoided if possible. If not, if the decision is made to vaccinate, providers should be prepared to treat immediate allergic reactions due to latex, including anaphylaxis. The most common type of latex hypersensitivity is a delayed-type (type 4, cell-mediated) allergic contact dermatitis. For patients with a history of contact allergy to latex, vaccines supplied in vials or syringes that contain dry natural rubber or natural rubber latex may be administered."

(ACIP General Best Practice Guidelines for Immunization)

Vaccine (Trade Name)	Package Insert Date	Latex (Yes/No)[a]
Adenovirus	10/2019	No
Anthrax (Biothrax)	11/2015	Yes
BCG (Tice)	02/2009	No
Cholera (Vaxchora)	06/2016	No
Dengue (Dengvaxia)	06/2019	No
DT (Sanofi)	06/2018	No
DTaP (Daptacel)	01/2021[b]	No
DTaP (Infanrix)	01/2021[b]	Yes – Syringe, No – Vial
DTaP-IPV (Kinrix)	01/2021[b]	Yes – Syringe, No – Vial
DTaP-IPV (Quadracel)	02/2021	No
DTaP-HepB-IPV (Pediarix)	01/2021[b]	Yes
DTaP-IPV/Hib (Pentacel)	12/2019	No
DTaP-IPV-Hib-HepB (Vaxelis)	10/2020	No
Ebola Zaire (ERVEBO)	01/2021[b]	No
Hib (ActHIB)	05/2019	No
Hib (Hiberix)	04/2018	No
Hib (PedvaxHIB)	01/2021[b]	Yes
Hep A (Havrix)	01/2021[b]	Yes – Syringe , No – Vial
Hep A (Vaqta)	01/2021[b]	Yes – Syringe, Yes – Vial
Hep B (Engerix-B)	01/2021[b]	Yes – Syringe, No – Vial
Hep B (Recombivax)	12/2018	Yes – Syringe, Yes – Vial
Hep B (Heplisav-B)	05/2020	No
Hep A/Hep B (Twinrix)	01/2021[b]	Yes
HPV (Gardasil 9)	08/2020	No
Influenza (Afluria) Quadrivalent[c]	07/2020	No
Influenza (Fluad) [c]	10/2020	No
Influenza (Fluad) Quadrivalent[c]	11/2020	No
Influenza (Fluarix) Quadrivalent[c]	07/2020	No
Influenza (Flublok) Quadrivalent[c]	06/2020	No
Influenza (Flucelvax) Quadrivalent[c]	03/2020	No
Influenza (Flulaval) Quadrivalent[c]	2020	No
Influenza (Fluzone) Quadrivalent[c]	2020	No
Influenza (Fluzone) High Dose[c]	2020	No
Influenza (FluMist) Quadrivalent[c]	08/2020	No

Appendix B

Vaccine (Trade Name)	Package Insert Date	Latex (Yes/No)[a]
IPV (Ipol)	01/2021[b]	No
Japanese Encephalitis (Ixiaro)	09/2018	No
MenACWY (Menactra)	04/2018	No
MenACWY(MenQuadfi)	01/2021[b]	No
MenACWY (Menveo)	07/2020	No
MenB (Bexsero)	01/2021[b]	Yes
MenB (Trumenba)	2018	No
MMR (M-M-R II)	12/2020	No
MMRV (ProQuad) (Frozen: Recombinant Albumin)	01/2021[b]	No
PCV13 (Prevnar 13)	08/2017	No
PPSV-23 (Pneumovax)	09/2020	No
Rabies (Imovax)	10/2019	No
Rabies (RabAvert)	2018	No
Rotavirus (RotaTeq)	01/2021[b]	No
Rotavirus (Rotarix)	01/2021[b]	Yes
Smallpox (Vaccinia) (ACAM2000)	03/2018	No
Td (Tenivac)	11/2019	Yes – Syringe, No – Vial
Td (TDVAX)	09/2018	No
Tdap (Adacel)	12/2020	Yes[d] – Syringe, No – Vial
Tdap (Boostrix)	09/2020	Yes – Syringe, No – Vial
Typhoid (Typhim Vi)	03/2020	No
Typhoid (Vivotif Ty21a)	09/2013	No
Varicella (Varivax) Frozen	01/2021[b]	No
Yellow Fever (YF-Vax)	02/2019	No
Zoster (Shingles) (Shingrix)	01/2021[b]	No

Abbreviations: DT = diphtheria and tetanus toxoids; DTaP = diphtheria and tetanus toxoids and acellular pertussis; Hep A = Hepatitis A; Hep B = Hepatitis B; Hib = *Haemophilus influenzae* type b; HPV = human papillomavirus; IPV = inactivated poliovirus; LAIV = live, attenuated influenza vaccine; MenACWY = quadrivalent meningococcal conjugate vaccine; MenB = serogroup B meningococcal vaccine; MMR = measles, mumps, and rubella; MMRV = measles, mumps, rubella, varicella; PCV13 = pneumococcal conjugate vaccine; PI = Package Insert; PPSV23= pneumococcal polysaccharide vaccine; Td = tetanus and diphtheria toxoids; Tdap = tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis.

[a] All information was extracted from manufacturers' package inserts. The date shown in the Date column of the table is the edition date of the PI is use in February 2020. If in doubt about whether a PI has been updated since this table was prepared, check the FDA's website at: http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm093833.htm

[b] The PI was not dated and this is the date the PI was reviewed for this table.

[c] All influenza vaccine in this table are 2020-21 northern hemisphere formulation.

[d] The most current PI (12/2020) indicates no latex in any presentation of Adacal. Previous PIs indicate tip caps of some lots of Adacel prefilled syringes contain latex while others do not. Check the package insert that came with your vaccine, if necessary.

January 2021

Quick Chart of Vaccine-Preventable Disease Terms in Multiple Languages

Eastern European Languages								
English	**Bosnian**	**Croatian**	**Polish**	**Romanian**	**Russian**	**Serbian**	**Slovak**	**Ukrainian**
DTP (DTaP)	Detepe	Detepe	DTaP	Di-Te-Per	АКДС	Detepe	DiTePe	
Diphtheria	Difterija	Difterije	Błonica	Difteriei	Дифтерия	Дифтерије	Diftéria; záškrt	Дифтерії
Haemophilus influenzae type b	Hemofilična influenca tipa B	Haemophilus influenzae tipa b	Haemophilus influenzae typu b	Haemophilus influenza tip b boala	Гемофильноя инфекция типа В	Хаемопхилус инфлуензае тип Б болести	Haemophilus influenza typ b; ochorenia	Гемофільної інфекції типу В захворювань
Hepatitis A	Žutica A, Hepatitis A	Žutica A, hepatitisa A	Wirusowe zapalenie wątroby typu A	Hepatita A	гепатит А	Хепатитиса А	Hepatitída A	Гепатиту S
Hepatitis B	Žutica B, Hepatitis B	Žutica B, hepatitisa B	Wirusowe zapalenie wątroby typu B	Hepatita B	гепатит В	Хепатитиса В	Hepatitída B	Гепатиту В
Human papillomavirus	Ljudski papiloma virus	Papilomavirusi čovjeka	Wirus brodawczaka ludzkiego	Papilomavirus uman	вирус папилломы человека	људски папилома вирус	L'udský papillomavírus	Вірус папіломи людини
Influenza	Gripa	Gripe	Grypa	Gripa	грипп	грип	Chrípka	Грипу
MMR	MMR					MMR		КПК
Measles	Rubeola	Ospice	Odra	Pojarul	корЬ	Мале богиње	Morbilli; Osýpky	іНФорМаціЯ про Кір
Meningococcal ACWY	Meningokokal ACWY	Meningokoknog ACWY	Meningokoki ACWY	Meningococice ACWY	менингококковая ACWY	Менингококне ACWY	Meningokokove ACWY	Менінгококова Сполучених
Mumps	Zauške	Zaušnjaci	Świnka	Oreionul, Oreion	Свинка, паротит	Эаушке	Priusnica	Кір
Pertussis	Veliki kašalj	Kašalj hripavac	Krztusiec	Tusei convulsive	Коклюша	Пертусис	Čierny kašeľ	Кашлюку
Poliomyelitis	Dječja paraliza	Dječje paralize	Paraliż dziecięcy	Poliomielita	полиомиелит	Полизомиелит	Detská obrna	Поліомієліту
Pneumococcal conjugate	Upala pluča	Pneumokoka konjugirano	Pneumokoki	Pneumococic conjugat	Конъюгированная пневмококковоя	Пнеумоцоццал коњунговане	Konjugovaná pneumokoková	Пневмококковой конъюгированной
Rotavirus	Rotavirus	Rotawirus	Rotawirus	Rotavirus	Ротавирус	Ротавирусна инфекција	Ротавирус	Ротавірусної
Rubella	Male boginje	Rubeola	Różyczka	Pojar German	Краснуха	Рубеола	Rubeola	Краснуха
Shingles (Herpes zoster)	Herpes zoster	Šindra	Półpasiec	Herpes zoster (zona zoster)	Опоясывающий лишай	Херпес зостер (појасни херпес)	Pásového oparu; Pásový opar	Оперізуючий герпес (Оперізуючий лишай)
Smallpox	Veliki boginje	Veliki boginje	Ospa	Variola, variolei	Оспа	Veliki boginje	Kiahne	Віспа
Tetanus	Tetanus	Tetanusa	Tężec	Tetanosului	столбняк	Тетануса	Tetanus	Правця
Tuberculosis	Tuberkuloza	Tuberkuloza	Gruźlica	Tuberculozei	Туберкулёз	Tuberkuloza	Tuberkulóza	Туберкульоз
Varicella (chickenpox)	Ospice	Vodene kozice	Ospa wietrzna	Varicelă	ветряная оспа (ветряная)	Варицелла (цхицкен богиње)	Ovčím kiahňam; Ovčie kiahne	Вітряної віспи (Вітрянка)

Quick Chart of Vaccine-Preventable Disease Terms in Multiple Languages

Western European Languages								
English	**Dutch**	**French**	**German**	**Italian**	**Norwegian**	**Portuguese**	**Spanish**	**Swedish**
DTP	DKTP	DT Coq, DTC				Tríplice		Trippel
Diphtheria	Difterie	Diphtérie	Diphtherie	Difterite	Difteri	Difteria	Difteria	Difteri
Haemophilus influenzae type b	Haemophilus influenzae b	Haemophilus influenzae de type b	Haemophilus influenzae type b	Haemophilus influenzae b	Haemophilus influenzae tipe b	Doenca Haemophilus influenzae tipo b	Hemófilo tipo b, Haemophilus influenzae tipo b	Haemophilus influenzae typ b
Hepatitis A	Hepatitis A	Hepatite A	Hepatitis A	Epatite A	Hepatitt A	Hepatite A	hepatitis A	Hepatit A
Hepatitis B	Hepatitis B	Hepatite B	Hepatitis B	Epatite B	Hepatitt B	Hepatite B	hepatitis B	Hepatit B
Human papillomavirus	Humaan papillovirus	Papillovirus humaines	Humanen papillovirus	Il papillovirus umano	Humant papillomavirus	Virus do papiloma humano	Virus del papiloma humano	Mänskliga papillovirus
Influenza (“flu”)	Griep	Grippe	Grippe	L’nfluenzae	Influensa	Gripe	Gripe	Influensa
MMR	BMR	ROR	MMR	MPR		VASPR	SRP	MPR
Measles	Mazelen	Rougeole	Masern	Morbillo	Meslinger	Sarampo	Sarampión, Sarampión comun	Mässling
Meningococcal ACWY	Meningokokken ACWY	Antiméningo-coque ACWY	Meningokokken ACWY	Meningococcico ACWY	Meningokokksyk-dom ACWY	Meningocóccica ACWY	Meningococo ACWY	Meningokockinfek-tion ACWY
Mumps	Bof	Oreillons	Ziegenpeter	Parotite	Kusma	Caçhumba	Paperas, Parotiditis	Påssjuka
Pertussis (Whooping cough)	Kinkhoest	Coqueluche	Keuchhusten	Pertosse (tosse asinina)	Kikhoste	Coqueluche	Coqueluche (Tos ferina)	Kikhosta
Poliomyelitis	Kinderverlamming	Poliomyélite	Kinderlähmung	Poliomielite	Poliomyelitt	Poliomielite, paralisia Infantil	Poliomielitis	Poliomyelitis
Pneumococcal conjugate	Pneumokokken conjugaat	Antipneumococ-cique conjugué	Pneumokokken konjugat	Pneumococcico coniugato	Pneumokokk komjugatvaksine	Pneumocócica conjugada	Antineumocócica conjugada	Konjugerat pneumokock
Rotavirus	Rotavirus	Rotavirus	Rotavirus	Rotavirus	Rotavirus	Rotavírus	Rotavirus	Rotavirus
Rubella	Rode hond	Rubéole	Röteln	Rosolia	Røde hunder	Rubéola (sarampo alamão)	Rubéola, Sarampión aleman	Röda hund
Shingles (Herpes zoster)	Gordelroos (herpes zoster)	Zona (l’herpès zoster)	Gürtelrose (herpes zoster)	Fuoco di Sant’Antonion (l’herpes zoster)	Helvetesild (herpes zoster)	Zona (herpes zoster)	Zona de matojos (herpes)	Bältros (herpes zoste)
Smallpox	Pokken	Variole	Pocken	Vaioloso	Kopper	Varíola	Viruela	Smittkopper
Tetanus	Stijfkramp	Tétanos	Wundstarrkrampf	Tetano	Stivkrampe	Tétano, Tetânica	Tétanos, Tetánica, Tétano	Stelkramp
Tuberculosis	Tering	Tuberculose	Tuberkulose	Tubercolosi	Tuberkulose	Tuberculose	Tuberculínica	Tuberkulos
Varicella (chickenpox)	Varicella (waterpekkea)	Varicelle	Varizellen (windpocken)	Varicella	Vannkopper	Varicella (catapora)	Varicela	Vattkopper

Resources for Vaccines

Vaccine Excipients

- Food and Drug Administration (FDA) Vaccine Package Inserts: https://www.fda.gov/vaccines-blood-biologics/vaccines/vaccines-licensed-use-united-states
- Thimerosal and Vaccines (FDA): https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/thimerosal-and-vaccines
- Thimerosal and Vaccines (CDC): https://www.cdc.gov/vaccinesafety/concerns/thimerosal/index.html
- Common Ingredients in U.S. Licensed Vaccines (FDA): https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/common-ingredients-us-licensed-vaccines
- Excipients in Vaccines per 0.5 mL dose (Johns Hopkins): https://www.vaccinesafety.edu/components-Excipients.htm

Interpreting Vaccines from Other Countries

- World Health Organization (WHO) Country Profiles: https://apps.who.int/immunization_monitoring/globalsummary

Appendix B

Appendix C: Vaccine Information Statements

Appendix C

You Must Provide Patients with Vaccine Information Statements (VISs) – It's Federal Law!

What are Vaccine Information Statements (VISs)?

Vaccine Information Statements (VISs) are documents produced by the Centers for Disease Control and Prevention (CDC), in consultation with panels of experts and parents, to properly inform vaccinees (or their parents/legal representatives) about the risks and benefits of each vaccine. VISs are not meant to replace interactions with healthcare providers, who should address any questions or concerns that the vaccinee (or parent/legal representative) may have.

Using VISs is legally required!

Federal law (under the National Childhood Vaccine Injury Act) requires a healthcare professional to provide a copy of the current VIS to an adult patient or to a child's parent/legal representative before vaccinating an adult or child with a dose of the following vaccines: diphtheria, tetanus, pertussis, measles, mumps, rubella, polio, hepatitis A, hepatitis B, *Haemophilus influenzae* type b (Hib), influenza, pneumococcal conjugate, meningococcal, rotavirus, human papillomavirus (HPV), or varicella (chickenpox).

Where to get VISs

All available VISs can be downloaded from the websites of the Immunization Action Coalition at www.immunize.org/vis or CDC at www.cdc.gov/vaccines/hcp/vis/index.html. Ready-to-copy versions may also be available from your state or local health department.

Translations: You can find VISs in more than 30 languages on the Immunization Action Coalition website at www.immunize.org/vis.

To obtain translations of VIS in languages other than English, go to www.immunize.org/vis.

According to CDC, the appropriate VIS must be given:

- Prior to the vaccination (and prior to each dose of a multi-dose series);
- Regardless of the age of the vaccinee;
- Regardless of whether the vaccine is given in a public or private healthcare setting.

Top 10 Facts About VISs

FACT 1 — It's federal law! You must provide current* VISs to all your patients before vaccinating them.

Federal law requires that VISs must be used for patients of **ALL ages** when administering these vaccines:

- DTaP (includes DT)
- Td and Tdap
- hepatitis A
- hepatitis B
- Hib
- HPV
- influenza (inactivated and live, intranasal)
- MMR and MMRV
- meningococcal (MenACWY, MenB)
- pneumococcal conjugate
- polio
- rotavirus
- varicella (chickenpox)

For the vaccines not covered under the National Childhood Vaccine Injury Act (i.e., adenovirus, anthrax, Japanese encephalitis, pneumococcal polysaccharide, rabies, typhoid, yellow fever, and zoster), providers are not required by federal law to use VISs unless they have been purchased under CDC contract. However, CDC recommends that VISs be used whenever these vaccines are given.

*Federal law allows up to 6 months for a new VIS to be used.

FACT 2 — VISs can be given to patients in a variety of ways.

In most medical settings, VISs are provided to patients (or their parents/legal representatives) in paper form. However, VISs also may be provided using electronic media. Regardless of the format used, the goal is to provide a current VIS just prior to vaccination.

CONTINUED ON NEXT PAGE ▶

Most current versions of VISs (table)

As of February 1, 2021, the most recent versions of the VISs are as follows:

Adenovirus	1/8/20	**MMRV**	8/15/19
Anthrax	1/8/20	**Multi-vaccine**	4/1/20
Cholera	10/30/19	**PCV13**	10/30/19
DTaP	4/1/20	**PPSV23**	10/30/19
Hepatitis A	7/28/20	**Polio**	10/30/19
Hepatitis B	8/15/19	**Rabies**	1/8/20
Hib	10/30/19	**Rotavirus**	10/30/19
HPV	10/30/19	**Td**	4/1/20
Influenza	8/15/19	**Tdap**	4/1/20
Japanese enceph	8/15/19	**Typhoid**	10/30/19
MenACWY	8/15/19	**Varicella**	8/15/19
MenB	8/15/19	**Yellow fever**	4/1/20
MMR	8/15/19	**Zoster**	10/30/19

A handy list of current VIS dates is also available at www.immunize.org/catg.d/p2029.pdf.

immunization action coalition
IAC
immunize.org

Saint Paul, Minnesota · 651-647-9009 · www.immunize.org · www.vaccineinformation.org

www.immunize.org/catg.d/p2027.pdf · Item #P2027 (2/21)

(For information on special circumstances involving vaccination of a child when a parent/legal representative is not available at the time of vaccination, see CDC's *Frequently Asked Questions* at www.cdc.gov/vaccines/hcp/vis/about/vis-faqs.html.)

Prior to vaccination, VIS may be:

- Provided as a paper copy
- Offered on a permanent, laminated office copy
- Downloaded by the vaccinee (parent/legal representative) to a smartphone or other electronic device (VISs have been specially formatted for this purpose)
- Made available to be read before the office visit, e.g., by giving the patient or parent a copy to take home during a prior visit, or telling them how to download or view a copy from the Internet. These patients must still be offered a copy in one of the formats described previously to read during the immunization visit, as a reminder.

Regardless of the way the patient is given the VIS to read, providers must still offer a copy (which can be an electronic copy) of each appropriate VIS to take home following the vaccination. However, the vaccinee may decline.

FACT 3 VISs are required in both public and private sector healthcare settings.

Federal law requires the use of VISs in both public and private sector settings, regardless of the source of payment for the vaccine.

FACT 4 You must provide a current VIS *before* a vaccine is administered to the patient.

A VIS provides information about the disease and the vaccine and must be given to the patient **before** a vaccine is administered. It is also acceptable to hand out the VIS well before administering vaccines (e.g., at a prenatal visit or at birth for vaccines an infant will receive during infancy), as long as you still provide a current VIS right before administering vaccines.

FACT 5 You must provide a current VIS for *each* dose of vaccine you administer.

The most current VIS must be provided before **each dose** of vaccine is given, including vaccines given as a series of doses. For example, if 5 doses of a single vaccine are required (e.g., DTaP), the patient (parent/legal representative) must have the opportunity to read the information on the VIS before each dose is given.

FACT 6 You must provide VISs whenever you administer combination vaccines.

If you administer a combination vaccine that does not have a stand-alone VIS (e.g., Kinrix, Quadracel, Pediarix, Pentacel, Twinrix) you should provide the patient with individual VISs for the component vaccines, or use the Multi-Vaccine VIS (see below).

The Multi-Vaccine VIS may be used in place of the individual VISs for DTaP, Hib, hepatitis B, polio, and pneumococcal when two or more of these vaccines are administered during the same visit. It may be used for infants as well as children through 6 years of age. The Multi-Vaccine VIS should not be used for adolescents or adults.

FACT 7 VISs should be given in a language/format that the recipient can understand, whenever possible.

For patients who don't read or speak English, the law requires that providers ensure all patients (parent/legal representatives) receive a VIS, regardless of their ability to read English. To obtain VISs in more than 30 languages, visit the Immunization Action Coalition website at www.immunize.org/vis. Providers can supplement VISs with visual presentations or oral explanations as needed.

FACT 8 Federal law does not require signed consent in order for a person to be vaccinated.

Signed consent is not required by federal law for vaccination (although some states may require it).

FACT 9 To verify that a VIS was given, providers must record in the patient's medical record (or permanent office log or file) the following information:

- The edition date of the VIS (found on the back at the right bottom corner)
- The date the VIS is provided (i.e., the date of the visit when the vaccine is administered)

In addition, providers must record:

- The office address and name and title of the person who administers the vaccine
- The date the vaccine is administered
- The vaccine manufacturer and lot number

FACT 10 VISs should not be altered before giving them to patients, but you can add some information.

Providers should not change a VIS or write their own VISs. However, it is permissible to add a practice's name, address, and contact information to an existing VIS.

Additional resources on VISs and their use are available from the following organizations:

Immunization Action Coalition

- *VIS general information and translations in more than 30 languages:* www.immunize.org/vis
- *Current Dates of Vaccine Information Statements:* www.immunize.org/catg.d/p2029.pdf

Centers for Disease Control and Prevention

- *VIS website:* www.cdc.gov/vaccines/hcp/vis
- *VIS Facts:* www.cdc.gov/vaccines/hcp/vis/about/facts-vis.html
- *VIS FAQs:* www.cdc.gov/vaccines/hcp/vis/about/vis-faqs.html

Immunization Action Coalition · Saint Paul, Minnesota · 651-647-9009 · www.immunize.org · www.vaccineinformation.org

www.immunize.org/catg.d/p2027.pdf · Item #P2027 (2/21)

Instructions for the Use of

Vaccine Information Statements

Required Use

1. Provide a Vaccine Information Statement (VIS) when a vaccination is given.

As required under the National Childhood Vaccine Injury Act (42 U.S.C. §300aa-26), all health care providers in the United States who administer, to any child or adult, any of the following vaccines — diphtheria, tetanus, pertussis, measles, mumps, rubella, polio, hepatitis A, hepatitis B, *Haemophilus influenzae* type b (Hib), influenza, pneumococcal conjugate, meningococcal, rotavirus, human papillomavirus (HPV), or varicella (chickenpox) — shall, prior to administration of each dose of the vaccine, provide a copy to keep of the relevant current edition vaccine information materials that have been produced by the Centers for Disease Control and Prevention (CDC):

- to the parent or legal representative[1] of any child to whom the provider intends to administer such vaccine,
  OR
- to any adult[2] to whom the provider intends to administer such vaccine.

If there is not a single VIS for a combination vaccine, use the VISs for all component vaccines.

VISs should be supplemented with visual presentations or oral explanations as appropriate.

2. Record information for each VIS provided.

Health care providers shall make a notation in each patient's permanent medical record at the time vaccine information materials are provided, indicating:

(1) the edition date of the Vaccine Information Statement distributed, and
(2) the date the VIS was provided.

This recordkeeping requirement supplements the requirement of 42 U.S.C. §300aa-25 that all health care providers administering these vaccines must record in the patient's permanent medical record (or in a permanent office log):

(3) the name, address and title of the individual who administers the vaccine,
(4) the date of administration, and
(5) the vaccine manufacturer and lot number of the vaccine used.

[1] "Legal representative" is defined as a parent or other individual who is qualified under State law to consent to the immunization of a minor child or incompetent adult.

[2] In the case of an incompetent adult, relevant VISs shall be provided to the individual's legal representative. If the incompetent adult is living in a long-term care facility, all relevant VISs may be provided at the time of admission, or at the time of consent if later than admission, rather than prior to each vaccination.

Applicability of State Law

Health care providers should consult their legal counsel to determine additional State requirements pertaining to immunization. The Federal requirement to provide the vaccine information materials supplements any applicable State laws.

Availability of Copies

Copies are available in English and many other languages from CDC's website at **www.cdc.gov/vaccines/pubs/vis**. Single camera-ready copies may also be available from State health departments.

Current VIS Editions

DTaP: 4/1/20†
Hib: 10/30/19†
Hepatitis A: 7/28/20†
Hepatitis B: 8/15/19†
HPV (Gardasil-9): 10/30/19†
Influenza (inactivated): 8/15/19†
Influenza (live): 8/15/19†
MMR: 8/15/19†
MMRV: 8/15/19†
Meningococcal ACWY: 8/15/19†
Meningococcal B: 8/15/19†
Pneumococcal (PCV13): 10/30/19†
Polio: 10/30/19†
Rotavirus: 10/30/19†
Td: 4/1/20†
Tdap: 4/1/20†
Varicella: 8/15/19†
Multi-Vaccine*: 4/1/20†

*An optional alternative when two or more routine childhood vaccines (i.e., DTaP, hepatitis B, Hib, pneumococcal, or polio are administered at the same visit.

†Interim

07/28/2020

42 U.S.C. § 300aa-26

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

C

Appendix C

Vaccine Information Statements: Frequently Asked Questions

For an updated list of VIS FAQs, visit: https://www.cdc.gov/vaccines/hcp/vis/about/vis-faqs.html

General Questions

Q: Are VISs "informed consent" forms?

A: No. People sometimes use the term "informed consent" loosely when referring to VISs. VISs are written to fulfill the information requirements of the National Childhood Vaccine Injury Act, not as informed consent forms. But because they cover both benefits and risks associated with vaccinations, they provide enough information that anyone reading them should be adequately informed.

Some states have informed consent laws, covering either procedural requirements (e.g., whether consent may be oral or must be written) or substantive requirements (e.g., types of information required). Check your state medical consent law to determine if there are any specific informed consent requirements relating to immunization. VISs may be used for informed consent as long as they conform to the appropriate state laws.

Q: Why is it recommended that the patient be given a copy of the VIS to take away following vaccination?

A: In addition to information about the vaccine's risks and benefits, VISs contain information that may be useful later (e.g., information about what to do in the case of an adverse reaction, and where to find additional information about the disease or vaccine). Patients may choose not to take the VIS, but the provider should offer them the opportunity.

Q: Why are the edition dates on some of the VISs so old? Are they obsolete? Why can't they be updated every year?

A: VISs are updated only when they need to be. For instance, a VIS would be updated if there were a change in ACIP recommendations that affects the vaccine's adverse event profile, indications, or contraindications. Knowing that VISs posted on CDC's VIS website are always current should help alleviate any concern. Annually changing the dates on VISs that haven't changed otherwise could be confusing too, because there could be multiple VISs in circulation that are identical but have different dates. Providers using paper VISs shouldn't be required to renew their stocks each year because the date changed.

Q: What is the reading level of VISs?

A: Defining the readability of a VIS by a quantitative "grade level" measure can be difficult and misleading, particularly for a document in which certain long words can't be avoided, and which is not formatted in a traditional block-text style. Applying a Flesch-Kincaid test to a VIS usually shows about a 10th grade reading level. Great care is taken to make VISs as easy to read and understand as possible, given the constraints imposed by the subject matter. When questioned, representative patients, including those considered "low-literacy," have reported finding VISs easy to understand.

Q: Some VISs contain recommendations that are at odds with the manufacturer's package insert. Why?

A: VISs are based on the ACIP's recommendations, which occasionally differ from those made by the manufacturer. These differences may involve adverse events. Package inserts generally tend to include all adverse events that were temporally associated with a vaccine during clinical trials, whereas ACIP tends to recognize only those believed to be causally linked to the vaccine.

Q: Should the VISs be used for adults getting vaccines as well as for children?

A: Yes. Anyone receiving a covered vaccine should be given the appropriate VIS. VISs are worded so they may be used by adults as well as children. Exceptions are VISs for vaccines that are not licensed for adults, such as DTaP or rotavirus.

Q: The law states that VISs may be given to a child's "legal representative." How is "legal representative" defined? Is it different from "legal guardian?"

A: "Legal representative" is a parent or other individual who is qualified under state law to consent to the immunization of a minor. It could include people other than the child's legal guardian.

Q: Where can I find the edition dates of past VISs?

A: See the list of edition dates of all past VISs, and vaccine information materials predating VISs.

Using Vaccine Information Statements

Q: How do we determine when a VIS must be given to a "legal representative" rather than to the patient? For example, if an 18-year old is considered a child, would it be illegal to give a VIS to him or her directly, as opposed to a parent or guardian?

A: The National Childhood Vaccine Injury Act does not define a "child" for purposes of the Act. "Legal representative" is defined as "a parent or an individual who qualifies as a legal guardian under State law." A reasonable interpretation is that State law, and specifically the State's medical consent law, should be deferred to for purposes of defining who is a minor. For example, if an 18 year old can consent to immunization under a State's law, that 18 year old is the person who should be provided a copy of the VIS.

Q: How should we distribute VISs when the parent or legal representative of a minor is not present at the time the vaccination is given, for example during a school-based adolescent vaccination program?

A: When parents/legal representatives are not present at the time of vaccination of a minor (e.g., school-located vaccination clinics held during school hours, school-based health centers), several challenges arise related to provision of Vaccine Information Statements (VISs). Please see the questions and answers below for guidance on how to address these challenges.

Q: How early can VISs be provided to parents/legal representatives prior to vaccination?

A: The National Childhood Vaccine Injury Act requires that a current VIS be provided to parents/legal representatives prior to vaccination. Although the Act does not specify the amount of time allowed between VIS provision and vaccination, they must be provided as close to the time of vaccination as is programmatically feasible and reasonable, keeping in mind that VISs are designed to inform vaccine recipients (or their parents/legal representatives) about the risks and benefits of specific vaccines, as well as medical eligibility, prior to vaccine receipt. For example, providing VISs several weeks prior to a scheduled school-located vaccination clinic may be reasonable. However, providing VISs several months prior to vaccination (e.g., providing them in July for a January vaccination clinic or at the end of one school year for a vaccination clinic the next school year) is not acceptable as parents/legal representatives may not have retained the VISs to review just prior to vaccination, the VIS may have since been revised, and a student's medical eligibility may have changed during that time.

Q: Is there a requirement to verify that parents/legal representatives have actually received and reviewed the VIS?

A: Yes. The mandatory instructions for use of the VIS require providers to make a notation in the patient's medical record or permanent office log regarding provision of the VIS. If VISs (paper or electronic) are not provided to parents/legal representatives at the time of vaccination, parents/legal representatives must acknowledge in writing (or electronically) receipt and review of the current VIS. This can be accomplished by including a written statement that the parent/legal representative received and reviewed the current edition of the VIS, with the edition date specified, on the medical consent form authorizing vaccination. The parent's/legal representative's signature (or electronic signature if allowed under state law) then verifies receipt/review. Where allowed under the applicable state medical consent law, such verification/consent can be accomplished through electronic means. The signed verification of receipt/review of the VIS must be retained by the clinic/health care provider in the same manner and for the same timeframe as other medical consents are required to be retained by health care providers under the state's medical consent law.

Q: What are the acceptable methods of VIS provision to parents/legal representatives?

A: If the parent/legal representative is present at the time of vaccination, the VIS (paper or electronic) must be provided to the parent/legal representative before the child is vaccinated. If the parent/legal representative is not present, provision of the VIS prior to vaccination must be coupled with a method to verify parent/legal representative receipt of the VIS, in addition to parent/legal representative consent to vaccination in compliance with the applicable state medical consent law. Some examples of methods of VIS provision are as follows*:

- Providing a physical copy of the VIS to the parent/legal representative;
- Providing a link to the VIS in a physical letter sent to the parent/legal representative;
- Providing the VIS as an attachment or weblink contained within an email sent to the parent/legal representative.

*As noted above, if not provided directly to the parent/legal representative at the time of vaccination, the VIS must be provided prior to vaccination along with a requirement to acknowledge receipt/review of the VIS. This requirement can be accomplished by adding a written statement that the parent/legal representative received and reviewed the current edition of the VIS, with the edition date specified, on the medical consent form authorizing vaccination. Where allowed under the applicable state medical consent law, such verification/consent can be accomplished through electronic means.

Q: Our state allows parents/legal representatives to provide a single, one-time consent for vaccines that require multiple doses given over weeks or months. In this case, do we have to provide a VIS prior to every dose administered?

A: Yes. Since a child's medical condition might change between doses, a VIS must be provided prior to administration of each dose to allow the parent to review the child's situation and determine whether or not to withdraw consent for additional doses. However, an additional acknowledged verification of receipt/review of the VIS and consent to vaccination for the following doses is not required if a single consent for a vaccine series is authorized under the applicable state medical consent law. In that instance, the original verification of receipt/review of the VIS and consent to the vaccination series sent prior to administration of the first dose must comply with any state medical consent requirement related to providing a process through which the parent/legal representative may later withdraw consent for additional doses, if such a requirement exists.

Q: How should we comply with the law for patients who cannot read the VISs (e.g., those who are illiterate or blind)?

A: The NCVIA requires providers to supplement the VISs with "visual presentations" or oral "explanations" as needed. If patients are unable to read the VISs, it is up to the provider to ensure that they have that information. VISs can be read to these patients, or videotapes can be used as supplements.

Q: How should we deal with combination vaccines for which there is not a VIS?

A: Unfortunately, it is impractical to produce VISs for all licensed combination vaccines. When administering a combination vaccine, one option is to use the individual VISs for each component. For example, when administering Pediarix, use the VISs for DTaP, hepatitis B, and polio.

A second option is to use the Pediatric Multi-vaccine VIS when the combination vaccine contains components that are part of that VIS (DTaP, hepatitis B, Hib, PCV13, and polio). Using the same example, the Pediatric Multi-vaccine VIS can be used when administering Pediarix, and will require only one VIS to be used, rather than three.

New and Updated VISs

Q: What should be done if there is not a VIS for a particular vaccine?

A: It is possible, particularly for a newly-approved vaccine, that the vaccine could become available before a VIS can be produced. The law does not require that a vaccine be withheld if a VIS for it does not yet exist. Until a VIS is available for a particular vaccine, a provider may use the manufacturer's package insert, written FAQs, or any other document – or produce their own information materials – to inform patients about the benefits and risks of that vaccine. Once a VIS is available it should be used; but providers should not delay use of a vaccine because of the absence of a VIS.

Q: When do we have to start using a new VIS?

A: The date for a new VIS's required use is announced when the final draft is published in the Federal Register. Ideally, providers will begin using a new VIS immediately. A provider might be reluctant to discard existing stocks of a VIS when a new edition is published. This will become less an issue as providers and patients begin to rely more on electronic, rather than paper, versions of VISs. As a general rule, when changes to a VIS concern the safety of the vaccine (e.g., contraindications or precautions, or adverse events), it is essential that the new edition be used immediately upon publication.

Q: What should we do if recommendations for a vaccine change but there is a delay in updating the appropriate VIS?

A: Production of a VIS can be held up for a variety of reasons. As we say for newly-approved vaccines, never withhold a vaccine because there is not a current VIS for it. The existing VIS should continue to be used, and the provider can supplement it, as appropriate, either verbally or with the manufacturer's package insert or other print materials.

The Pediatric Multi-Vaccine VIS

Q: May the existing, single-vaccine VISs still be used?

A: Yes. The Multi-Vaccine VIS is an optional alternative to existing VISs. Providers wishing to continue using the individual VISs may do so. These will continue to be updated when recommendations change.

Q: When we record the edition date of the VISs on the patient's medical record, do we record the date on the Multi-Vaccine VIS or the dates on the individual VISs?

A: When you use the Multi-Vaccine VIS, record its date for each vaccine given. If there is ever a question, this will make it clear that this VIS was used, and not the individual VISs.

Q: Can the Multi-Vaccine VIS be used for children older than 6 months, or for adolescents or adults getting any of these vaccines?

A: It may be used for older children getting two or more of these vaccines during the same visit (e.g., a 12-month old getting Hib and PCV or a 4-year old getting DTaP and IPV). It should not be used for adolescents or adults.

Q: If a single-vaccine VIS is updated before the Multi-Vaccine VIS, may the multi continue to be used for that vaccine?

A: Sometimes there can be delays in updating a VIS. If an individual VIS for a vaccine covered on the multi gets updated before the multi does, the multi may still be used. You may give the patient the new single VIS at the same time, or explain verbally or with other written materials any changes. This is most important if the changes involve contraindications or adverse events; in these cases be certain the patient gets up-to-date information. It is less important if the update reflects other changes, such as changes in the routine schedule.

Appendix C

Additional Resources for Vaccine Information Statements

Below is a list of additional resources for Vaccine Information Statements (VISs) as recommended.

- Vaccine Information Statements (VISs): https://www.cdc.gov/vaccines/hcp/vis/index.html
- Current VISs: https://www.cdc.gov/vaccines/hcp/vis/current-vis.html
- About VISs: https://www.cdc.gov/vaccines/hcp/vis/about/index.html
- Dates of Current and Past Vaccine Information Materials: https://www.cdc.gov/vaccines/hcp/vis/vis-dates.html
- Barcodes on Vaccine Information Statements: https://www.cdc.gov/vaccines/hcp/vis/barcodes.html

Appendix D: Vaccine Safety

Appendix D

Vaccine Adverse Event Reporting System (VAERS)

VAERS is a national post-licensure vaccine safety surveillance program co-managed by the Centers for Disease Control and Prevention (CDC) and the U.S. Food and Drug Administration (FDA). VAERS serves as an early warning system to detect possible safety issues with U.S. vaccines by collecting information about adverse events (possible side effects or health problems) that occur after vaccination. A report to VAERS does not indicate that a vaccine caused an adverse event, only that the adverse event occurred sometime after vaccination.

Who can report?

Anyone can submit a report to VAERS — healthcare professionals, vaccine manufacturers, and the general public. VAERS welcomes all reports, regardless of seriousness, and regardless of how likely the vaccine may have been to have caused the adverse event.

What should be reported?

Healthcare providers are **required by law** to report:

- Any adverse event listed by the vaccine manufacturer as a contraindication to subsequent doses of the vaccine
- Any adverse event listed in the Reportable Events Table that occurs within the specified time period after the vaccination.

Healthcare providers are strongly **encouraged** to report:

- Any adverse event that occurs after the administration of a vaccine licensed in the United States, whether it is or is not clear that a vaccine caused the adverse event
- Vaccine administration errors

A copy of the Reportable Events Table can be found on the following page, or at https://vaers.hhs.gov/resources/infoproviders.html

Note: COVID-19 vaccines under an Emergency Use Authorization have additional VAERS reporting requirements. See https://vaers.hhs.gov/faq.html.

How do I report?

There are two ways to report to VAERS:

Option 1: Online (preferred). Submit a VAERS report using the online reporting tool at https://vaers.hhs.gov/esub/index.jsp

Before you begin, review the Checklist for Completing the VAERS form at https://vaers.hhs.gov/reportevent.html. Information submitted using the online reporting tool is transmitted securely to VAERS.

Option 2: Writeable PDF Form. Download the writable PDF form (located at https://vaers.hhs.gov/uploadFile/index.jsp) to your computer, complete it, and then return to the VAERS website to upload the completed form. It is important that you use a desktop or laptop computer on which you can securely save a document that contains protected health information, personal identifiers or other sensitive personal or patient information. When you upload the form, the information is transmitted securely to VAERS.

Appendix D

What are the strengths and limitations of VAERS data?

When evaluating VAERS data, it is important to understand the strengths and limitations. VAERS data contain both coincidental events and those truly caused by vaccines.

Strengths:

- VAERS collects national data from all U.S. states and territories.
- VAERS accepts reports from anyone.
- The VAERS form collects information about the vaccine, the person vaccinated, and the adverse event.
- Data are publicly available.
- VAERS can be used as an early warning system to identify rare adverse events.
- It is possible to follow-up with patients to obtain health records, when necessary.

Limitations

- It is generally not possible to find out from VAERS data if a vaccine caused the adverse events.
- Reports submitted to VAERS often lack details and sometimes contain errors.
- Serious adverse events are more likely to be reported than mild side effects.
- Rate of reports may increase in response to media attention and increase public awareness.
- It is not possible to use VAERS data to calculate how often an adverse event occurs in a population.

Where can I find more information?

If you need further assistance with reporting to VAERS, please email info@vaers.org or call 1-800-822-7967. Operators are on duty from 9:00 a.m. to 5:00 p.m., Eastern Time, Monday through Friday.

For more information, visit the VAERS website at https://vaers.hhs.gov/

VAERS Table of Reportable Events Following Vaccination*

Vaccine/Toxoid	Event and Interval ** from Vaccination
Tetanus in any combination: DTaP, DTP, DTP-Hib, DT, Td, TT, Tdap, DTaP-IPV, DTaP-IPV/Hib, DTaP-HepB-IPV	A. Anaphylaxis or anaphylactic shock (7 days) B. Brachial neuritis (28 days) C. Shoulder Injury Related to Vaccine Administration (7 days) D. Vasovagal syncope (7 days) E. Any acute complications or sequelae (including death) of above events (interval - not applicable) F. Events described in manufacturer's package insert as contraindications to additional doses of vaccine (interval - see package insert)
Pertussis in any combination: DTaP, DTP, DTP-Hib, Tdap, DTaP-IPV, DTaP-IPV/Hib, DTaP-HepB-IPV	A. Anaphylaxis or anaphylactic shock (7 days) B. Encephalopathy or encephalitis (7 days) C. Shoulder Injury Related to Vaccine Administration (7 days) D. Vasovagal syncope (7 days) E. Any acute complications or sequelae (including death) of above events (interval - not applicable) F. Events described in manufacturer's package insert as contraindications to additional doses of vaccine (interval - see package insert)
Measles, mumps and rubella in any combination: MMR, MMRV, MM	A. Anaphylaxis or anaphylactic shock (7 days) B. Encephalopathy or encephalitis (15 days) C. Shoulder Injury Related to Vaccine Administration (7 days) D. Vasovagal syncope (7 days) E. Any acute complications or sequelae (including death) of above events (interval - not applicable F. Events described in manufacturer's package insert as contraindications to additional doses of vaccine (interval - see package insert)
Rubella in any combination: MMR, MMRV	A. Chronic arthritis (42 days) B. Any acute complications or sequelae (including death) of above event (interval - not applicable) C. Events described in manufacturer's package insert as contraindications to additional doses of vaccine (interval - see package insert)
Measles in any combination: MMR, MMRV, MM	A. Thrombocytopenic purpura (7-30 days) B. Vaccine-strain measles viral infection in an immunodeficient recipient • Vaccine-strain virus identified (interval – not applicable) • If strain determination is not done or if laboratory testing is inconclusive (12 months) C. Any acute complications or sequelae (including death) of above events (interval - not applicable) D. Events described in manufacturer's package insert as contraindications to additional doses of vaccine (interval - see package insert)
Oral Polio (OPV)	A. Paralytic polio • in a non-immunodeficient recipient (30 days) • in an immunodeficient recipient (6 months) • in a vaccine-associated community case (interval - not applicable) B. Vaccine-strain polio viral infection • in a non-immunodeficient recipient (30 days) • in an immunodeficient recipient (6 months) • in a vaccine-associated community case (interval - not applicable) C. Any acute complication or sequelae (including death) of above events (interval - not applicable) Events described in manufacturer's package insert as contraindications to additional doses of vaccine (interval - see package insert) D. Events described in manufacturer's package insert as contraindications to additional doses of vaccine (interval - see package insert)

Appendix D

Vaccine/Toxoid	Event and Interval ** from Vaccination
Inactivated Polio in any combination: IPV, DTaP-IPV, DTaP-IPV/Hib, DTaP-HepB-IPV	A. Anaphylaxis or anaphylactic shock (7 days) B. Shoulder Injury Related to Vaccine Administration (7 days) C. Vasovagal syncope (7 days) D. Any acute complication or sequelae (including death) of above events (interval - not applicable) E. Events described in manufacturer's package insert as contraindications to additional doses of vaccine (interval - see package insert)
Hepatitis B in any combination: HepB, HepA-HepB, DTaP-HepB-IPV, Hib-HepB	A. Anaphylaxis or anaphylactic shock (7 days) B. Shoulder Injury Related to Vaccine Administration (7 days) C. Vasovagal syncope (7 days) D. Any acute complications or sequelae (including death) of above events (interval - not applicable) E. Events described in manufacturer's package insert as contraindications to additional doses of vaccine (interval - see package insert)
***Haemophilus influenzae* type b in any combination (conjugate): Hib, Hib-HepB, DTaP-IPV/Hib, Hib-MenCY**	A. Shoulder Injury Related to Vaccine Administration (7 days) B. Vasovagal syncope (7 days) C. Any acute complication or sequelae (including death) of above events (interval - not applicable) D. Events described in manufacturer's package insert as contraindications to additional doses of vaccine (interval - see package insert)
Varicella in any combination: VAR, MMRV	A. Anaphylaxis or anaphylactic shock (7 days) B. Disseminated varicella vaccine-strain viral disease • Vaccine-strain virus identified (time interval unlimited) • If strain determination is not done or if laboratory testing is inconclusive (42 days) C. Varicella vaccine-strain viral reactivation (time interval unlimited) D. Shoulder Injury Related to Vaccine Administration (7 days) E. Vasovagal syncope (7 days) F. Any acute complication or sequelae (including death) of above events (interval - not applicable) G. Events described in manufacturer's package insert as contraindications to additional doses of vaccine (interval - see package insert)
Rotavirus (monovalent or pentavalent) RV1, RV5	A. Intussusception (21 days) B. Any acute complication or sequelae (including death) of above events (interval - not applicable) C. Events described in manufacturer's package insert as contraindications to additional doses of vaccine (interval - see package insert)
Pneumococcal conjugate (7-valent or 13-valent) PCV7, PCV13	A. Shoulder Injury Related to Vaccine Administration (7 days) B. Vasovagal syncope (7 days) C. Any acute complication or sequelae (including death) of above events (interval - not applicable) D. Events described in manufacturer's package insert as contraindications to additional doses of vaccine (interval - see package insert)
Hepatitis A in any combination: HepA, HepA-HepB	A. Shoulder Injury Related to Vaccine Administration (7 days) B. Vasovagal syncope (7 days) C. Any acute complication or sequelae (including death) of above events (interval - not applicable) D. Events described in manufacturer's package insert as contraindications to additional doses of vaccine (interval - see package insert)
Seasonal influenza (trivalent inactivated influenza, quadrivalent inactivated influenza, live attenuated influenza): IIV, IIV3, IIV4, RIV3, ccIIV3, LAIV4	A. Anaphylaxis or anaphylactic shock (7 days) B. Shoulder Injury Related to Vaccine Administration (7 days) C. Vasovagal syncope (7 days) D. Guillain-Barré Syndrome (42 days) E. Any acute complication or sequelae (including death) of above events (interval - not applicable) F. Events described in manufacturer's package insert as contraindications to additional doses of vaccine (interval - see package insert)

Vaccine/Toxoid	Event and Interval ** from Vaccination
Meningococcal: MCV4, MPSV4, Hib-MenCY, MenACWY, MenB	A. Anaphylaxis or anaphylactic shock (7 days) B. Shoulder Injury Related to Vaccine Administration (7 days) C. Vasovagal syncope (7 days) D. Any acute complication or sequelae (including death) of above events (interval - not applicable) E. Events described in manufacturer's package insert as contraindications to additional doses of vaccine (interval - see package insert)
Human Papillomavirus (quadrivalent, bivalent, or 9 valent): 9vHPV, 4vHPV, 2vHPV	A. Anaphylaxis or anaphylactic shock (7 days) B. Shoulder Injury Related to Vaccine Administration (7 days) C. Vasovagal syncope (7 days) D. Any acute complication or sequelae (including death) of above events (interval - not applicable) E. Events described in manufacturer's package insert as contraindications to additional doses of vaccine (interval - see package insert)
Any new vaccine recommended by the Centers for Disease Control and Prevention for routine administration to children.	A. Shoulder Injury Related to Vaccine Administration (7 days) B. Vasovagal syncope (7 days) C. Any acute complication or sequelae (including death) of above events (interval - not applicable) D. Events described in manufacturer's package insert as contraindications to additional doses of vaccine (interval - see package insert)

* Effective date: March 21, 2017. The Reportable Events Table (RET) reflects what is reportable by law (42 USC 300aa-25) to the Vaccine Adverse Event Reporting System (VAERS) including conditions found in the manufacturer package insert. In addition, healthcare professionals are encouraged to report any clinically significant or unexpected events (even if not certain the vaccine caused the event) for any vaccine, whether or not it is listed on the RET. Manufacturers are also required by regulation (21CFR 600.80) to report to the VAERS program all adverse events made known to them for any vaccine.

Note that the RET differs from the Vaccine Injury Table (VIT) regarding timeframes of adverse events. Timeframes listed on the RET reflect what is required for reporting, but not what is required for compensation. To view timeframes for compensation, please see the VIT at https://www.hrsa.gov/sites/default/files/vaccinecompensation/vaccineinjurytable.pdf.

**Represents the onset interval between vaccination and the adverse event. For a detailed explanation of terms, see the Vaccine Injury Table at https://www.hrsa.gov/sites/default/files/vaccinecompensation/vaccineinjurytable.pdf.

YOU CALL THE SHOTS

Vaccine Administration: Preventing Vaccine Administration Errors

A vaccine administration error is any preventable event that may cause or lead to inappropriate medication use or patient harm.[1] Vaccine administration errors can have many consequences, including inadequate immunological protection, possible injury to the patient, cost, inconvenience, and reduced confidence in the health care delivery system. Take preventive actions to avoid vaccine administration errors and establish an environment that values reporting and investigating errors as part of risk management and quality improvement.

Vaccine administration errors may be due to causes such as:

- Insufficient staff training
- Distraction
- Changes in recommendations
- Lack of standardized protocols
- Patient misidentification
- Using nonstandard or error-prone abbreviations
- Easily misidentified products (e.g. DTaP, DT, Tdap, Td)

If an error occurs, determine how the error occurred and take the appropriate actions to put strategies in place to prevent it from happening in the future. The following table outlines common vaccine administration errors and possible preventive actions you can take to avoid errors.

Error(s)	Possible Preventive Actions
Wrong vaccine, route, site, or dosage (amount); or improperly prepared.	Circle important information on the packaging to emphasize the difference between the vaccines.
	Include the brand name with the vaccine abbreviation whenever possible (e.g., PCV13 [Prevnar13]) in orders, medical screens, etc.
	Separate vaccines into bins or other containers according to type and formulation. Use color-coded identification labels on vaccine storage containers.
	Store look-alike vaccines in different areas of the storage unit (e.g., pediatric and adult formulations of the same vaccine on different shelves in the unit).
	Do not list vaccines with look-alike names sequentially on computer screens, order forms, or medical records, if possible.
	Consider using "name alert" or "look-alike" stickers on packaging and areas where these vaccines are stored.
	Consider purchasing products with look-alike packaging from different manufacturers, if possible.
	Establish "Do NOT Disturb" or no-interruption areas or times when vaccines are being prepared or administered.
	Prepare vaccine for one patient at a time. Once prepared, label the syringe with vaccine name.
	Do not administer vaccines prepared by someone else.
	Triple-check work before administering a vaccine and ask another staff member to check.
	Keep reference materials on recommended sites, routes, and needle lengths for each vaccine used in your facility in the medication preparation area.
	Clearly identify diluents if the manufacturer's label could mislead staff into believing the diluent is the vaccine itself.
	Integrate vaccine administration training into orientation and other appropriate education requirements.
	Provide education when new products are added to inventory or recommendations are updated.
	Use standing orders, if appropriate.

1. National Coordinating Council for Medication Error Reporting and Prevention, https://www.nccmerp.org/about-medication-errors

07/09/2021 CS 322033-A

Vaccine Administration: Preventing Vaccine Administration Errors

Error(s)	Possible Preventive Actions
Wrong patient	Verify the patient's identity before administering vaccines.
	Educate staff on the importance of avoiding unnecessary distractions or interruptions when staff is administering vaccine.
	Prepare and administer vaccines to one patient at a time. If more than one patient needs vaccines during the same clinical encounter (e.g., parent with two children), assign different providers to each patient, if possible. Alternatively, bring only one patient's vaccines into the treatment area at a time, labeled with vaccine and patient name.
Documentation errors	Do not use error-prone abbreviations to document vaccine administration (e.g., use intranasal route [NAS] to document the intranasal route—not IN, which is easily confused with IM).
	Use ACIP vaccine abbreviations.
	Change the appearance of look-alike names or generic abbreviations on computer screens, if possible.
Improperly stored and/or handled vaccine administered (e.g., expired vaccine given)	Integrate vaccine storage and handling training based on manufacturer guidance and/or requirements.
	Rotate vaccines so those with the earliest expiration dates are in the front of the storage unit. Use these first.
	Remove expired vaccines/diluents from storage units and areas where viable vaccines are stored.
	Isolate vaccines exposed to improper temperatures and contact the state or local immunization program and/or the vaccine manufacturer.
Scheduling errors (e.g., vaccine doses in a series administered too soon)	Use standing orders, if appropriate.
	Create procedures to obtain a complete vaccination history using the immunization information system (IIS), previous medical records, and personal vaccination records.
	Integrate vaccine administration training, including timing and spacing of vaccines, into orientation and other appropriate education requirements.
	For children, especially infants, schedule immunization visits after the birthday.
	Post current immunization schedules for children and adults that staff can quickly reference in clinical areas where vaccinations may be prescribed and administered.
	Post reference sheets for timing and spacing in your medication preparation area. CDC has vaccine catch-up guidance for DTaP, Tdap, Hib, PCV13, and polio vaccines to assist health care personnel in interpreting the catch-up schedule for children.
	Counsel parents and patients on how important it is for them to maintain immunization records.

Adapted with appreciation from Table 11-2, Medication Errors, 2nd ed, by Cohen, Michael. Washington D.C: American Pharmacists Association; 2007.

Healthcare providers are strongly encouraged to report vaccine administration errors to Vaccine Adverse Event Reporting System (VAERS).* To file an electronic report, please see the VAERS website at https://vaers.hhs.gov/reportevent.html

* At this time, COVID-19 vaccination has additional VAERS reporting requirements, including required reporting of vaccine administration errors. Please see https://vaers.hhs.gov/faq.html for more information.

07/09/2021 CS 322033-A

Appendix D

Vaccine Injury Compensation Program (VICP)

The VICP is a no-fault alternative to the traditional tort system for resolving vaccine injury claims. It was established as part of the National Childhood Vaccine Injury Act of 1986, after lawsuits against vaccine manufacturers and healthcare providers threatened to cause vaccine shortages and reduce vaccination rates. It provides compensation to people found to be injured by certain vaccines.

The VICP is administered jointly by the U.S. Department of Health and Human Services (HHS), the U.S. Court of Federal Claims (the Court), and the U.S. Department of Justice (DOJ). The VICP is located in the HHS, Health Resources and Services Administration (HRSA), Healthcare Systems Bureau, Division of Vaccine Injury Compensation.

Who can file a petition?

According to the Health Resources and Services Administration of HHS, a person may file a petition if they:

- received a vaccine covered by the VICP and believe that they have been injured by this vaccine
- are a parent or legal guardian of a child or disabled adult who received a covered vaccine and who they believe was injured by this vaccine
- are the legal representative of the estate of a deceased person who received a covered vaccine and who they believe was injured by the vaccine and/or whose death they believe resulted from the vaccine injury

You may file a petition regardless of age and United States citizenship. The covered vaccine must have been given in the United States or its territories with few exceptions. To learn more about exceptions, see the VICP website (https://www.hrsa.gov/vaccine-compensation/eligible/index.html).

In addition, to be eligible to file a claim, the effects of the person's injury must have:

1. lasted for more than 6 months after the vaccine was given; or
2. resulted in a hospital stay **and** surgery; or
3. resulted in death.

What vaccines are covered?

The **Vaccine Injury Table** makes it easier for some people to get compensation. The Table lists and explains injuries and conditions that are presumed to be caused by vaccines. It also lists time periods in which the first symptom of these injuries and conditions must occur after receiving the vaccine. If the first symptom of these injuries/conditions occurs within the listed time periods, it is presumed that the vaccine was the cause of the injury or condition unless another cause is found. For example, if a patient received the tetanus vaccine and had a severe allergic reaction (anaphylaxis) within 4 hours after receiving the vaccine, then it is presumed that the tetanus vaccine caused the injury, if no other cause is found.

If an injury or condition is not on the Table or if it did not occur within the time period on the Table, the petitioner must prove that the vaccine caused the injury or condition.

A copy of the Vaccine Injury Table is on the following page or can be found online at https://www.hrsa.gov/sites/default/files/hrsa/vaccine-compensation/vaccine-injury-table.pdf. A comprehensive explanation of terms used in the table accompanies the online version.

How can a petition be filed?

To learn how to file a petition, see the VICP website at https://www.hrsa.gov/vaccine-compensation/how-to-file/index.html

For more information, visit the VICP website at https://www.hrsa.gov/vaccine-compensation/index.html

National Childhood Vaccine Injury Act: Vaccine Injury Table

This table, supplemented with definitions and other explanatory material, can be found on the National Vaccine Injury Compensation Program's website at https://www.hrsa.gov/vaccinecompensation/vaccineinjurytable.pdf.

Vaccine	Illness, disability, injury or condition covered	Time period for first symptom or manifestation of onset or of significant aggravation after vaccine administration
I. Vaccines containing tetanus toxoid (e.g., DTaP, DTP, DT, Td, or TT)	A. Anaphylaxis	≤4 hours
	B. Brachial Neuritis	2-28 days (not less than 2 days and not more than 28 days)
	C. Shoulder Injury Related to Vaccine Administration	≤48 hours
	D. Vasovagal syncope	≤1 hour
II. Vaccines containing whole cell pertussis bacteria, extracted or partial cell pertussis bacteria, or specific pertussis antigen(s) (*e.g.,* DTP, DTaP, P, DTP-Hib)	A. Anaphylaxis	≤4 hours
	B. Encephalopathy or encephalitis	≤72 hours
	C. Shoulder Injury Related to Vaccine Administration	≤48 hours
	D. Vasovagal syncope	≤1 hour
III. Vaccines containing measles, mumps, and rubella virus or any of its components (*e.g.,* MMR, MM, MMRV)	A. Anaphylaxis	≤4 hours
	B. Encephalopathy or encephalitis	5-15 days (not less than 5 days and not more than 15 days)
	C. Shoulder Injury Related to Vaccine Administration	≤48 hours
	D. Vasovagal syncope	≤1 hour
IV. Vaccines containing rubella virus (*e.g.,* MMR, MMRV)	A. Chronic arthritis	7-42 days (not less than 7 days and not more than 42 days)
V. Vaccines containing measles virus (*e.g.,* MMR, MM, MMRV)	A. Thrombocytopenic purpura	7-30 days (not less than 7 days and not more than 30 days)
	B. Vaccine-Strain Measles Viral Infection in an immunodeficient recipient: • Vaccine-strain virus identified	Not applicable
	Vaccine-Strain Measles Viral Infection in an immunodeficient recipient: • If strain determination is not done or if laboratory testing is inconclusive	≤12 months

Vaccine	Illness, disability, injury or condition covered	Time period for first symptom or manifestation of onset or of significant aggravation after vaccine administration
VI. Vaccines containing polio live virus (OPV)	A. Paralytic Polio • in a non-immunodeficient recipient	≤30 days
	Paralytic Polio • in an immunodeficient recipient	≤6 months
	Paralytic Polio • in a vaccine associated community case	Not applicable
	B. Vaccine-Strain Polio Viral Infection • in a non-immunodeficient recipient	≤30 days
	Vaccine-Strain Polio Viral Infection • in an immunodeficient recipient	≤6 months
	Vaccine-Strain Polio Viral Infection • in a vaccine associated community case	Not applicable
VII. Vaccines containing polio inactivated virus (e.g., IPV)	A. Anaphylaxis	≤4 hours
	B. Shoulder Injury Related to Vaccine Administration	≤48 hours
	C. Vasovagal syncope	≤1 hour
VIII. Hepatitis B vaccines	A. Anaphylaxis	≤4 hours
	B. Shoulder Injury Related to Vaccine Administration	≤48 hours
	C. Vasovagal syncope	≤1 hour
IX. *Haemophilus influenzae* type b (Hib) vaccines	A. Shoulder Injury Related to Vaccine Administration	≤48 hours
	B. Vasovagal syncope	≤1 hour
X. Varicella vaccines	A. Anaphylaxis	≤4 hours
	B. Disseminated varicella vaccine-strain viral disease: • Vaccine-strain virus identified	Not applicable
	Disseminated varicella vaccine-strain viral disease: • If strain determination is not done or if laboratory testing is inconclusive	7-42 days (not less than 7 days and not more than 42 days)
	C. Varicella vaccine-strain viral reactivation	Not applicable
	D. Shoulder Injury Related to Vaccine Administration	≤48 hours
	E. Vasovagal syncope	≤1 hour
XI. Rotavirus vaccine	A. Intussusception	1-21 days (not less than 1 day and not more than 21 days)
XII. Pneumococcal conjugate vaccines	A. Shoulder Injury Related to Vaccine Administration	≤48 hours
	B. Vasovagal syncope	≤1 hour
XIII. Hepatitis A vaccines	A. Shoulder Injury Related to Vaccine Administration	≤48 hours
	B. Vasovagal syncope	≤1 hour

Vaccine	Illness, disability, injury or condition covered	Time period for first symptom or manifestation of onset or of significant aggravation after vaccine administration
XIV. Seasonal influenza vaccines	A. Anaphylaxis	≤4 hours
	B. Shoulder Injury Related to Vaccine Administration	<48 hours
	C. Vasovagal syncope	≤1 hour
	D. Guillain-Barré Syndrome	3-42 days (not less than 3 days and not more than 42 days)
XV. Meningococcal vaccines	A. Anaphylaxis	≤4 hours
	B. Shoulder Injury Related to Vaccine Administration	≤48 hours
	C. Vasovagal syncope	≤1 hour
XVI. Human papillomavirus (HPV) vaccines	A. Anaphylaxis	≤4 hours
	B. Shoulder Injury Related to Vaccine Administration	≤48 hours
	C. Vasovagal syncope	≤1 hour
XVII. Any new vaccine recommended by the Centers for Disease Control and Prevention for routine administration to children, after publication by the Secretary of a notice of coverage	A. Shoulder Injury Related to Vaccine Administration	≤48 hours
	B. Vasovagal syncope	≤1 hour

(Applies Only to Petitions for Compensation Filed under the National Vaccine Injury Compensation Program on or after March 21, 2017)

Last revised January 2021

Appendix D

Countermeasures Injury Compensation Program (CICP)

The Countermeasures Injury Compensation Program (CICP) is a Federal program that provides benefits for serious injuries that occur as a result of the administration or use of a covered countermeasure. Countermeasures are vaccines, antivirals, drugs, biologics, or medical devices used to diagnose, prevent, or treat, a declared pandemic, epidemic, or security threat. The Secretary of the United States Department of Health and Human Services (the Secretary) declares specific countermeasures under CICP.

This Program was established by the Public Readiness and Emergency Preparedness Act of 2005 (PREP Act), 42 U.S.C. § 247d-6e. The PREP Act also confers broad liability protections covering the manufacture, testing, development, distribution, or use of the designated covered countermeasure.

Some examples of covered public health threats are:

- COVID-19
- Ebola
- Pandemic Influenza A
- Smallpox
- Anthrax.

Who is eligible?

The following may be eligible:

- The injured countermeasure recipient
- Certain survivor(s) of a deceased injured countermeasure recipient
- The estate of a deceased injured countermeasure recipient

How can a claim be filed?

Individuals have one year from the date the vaccine or other covered countermeasure was administered or used to request compensation benefits. If their injury is added to a Countermeasures Injury Table, then they may also have one year from the effective date of the Table addition to file. To file a claim, individuals must submit a Request for Benefits Form and the Authorization for Use or Disclosure of Health Information Form to request medical records from each health care provider who treated the injured person. In addition, medical records from one year before the injury to the present time must be submitted.

For more detailed instructions, visit the CICP website at https://www.hrsa.gov/cicp/filing-benefits.

Eligible individuals may be compensated for certain reasonable and necessary medical expenses and for lost employment income at the time of the injury. Death benefits may be paid to certain survivors of covered countermeasures recipients who have died as a direct result of the covered countermeasure injury. The U.S. Department of Health and Human Services is the payer of last resort. Therefore, payments are reduced by those of other third-party payers.

Contact Information

Website: http://www.hrsa.gov/cicp/

E-mail: CICP@hrsa.gov

Phone: 1-855-266-CICP (2427)

Updated January 2021

Additional Resources for Vaccine Safety

Below is a list of additional resources for Vaccine Information Statements (VISs) as recommended.

General Vaccine Safety

- Vaccine Safety: https://www.cdc.gov/vaccinesafety/index.html
- Vaccine Safety Information for Healthcare Providers: https://www.cdc.gov/vaccinesafety/hcproviders/index.html

Safety Monitoring Systems

- Vaccine Adverse Event Reporting System (VAERS): https://vaers.hhs.gov/index.html
- Vaccine Safety Datalink (VSD): https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vsd/index.html

Clinical Immunization Safety Assessment (CISA) Project:

- https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/cisa/index.html

Compensation Programs

- Countermeasures Injury Compensation Program (CICP): https://www.hrsa.gov/cicp
- National Vaccine Injury Compensation Program (VICP): https://www.hrsa.gov/vaccine-compensation/index.html

Appendix D