D Immunization

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The two most effective means of preventing disease, disability, and death from infectious diseases have been sanitation and immunization.[1] Both approaches antedated understanding of the germ theory of disease. Artificial induction of immunity began centuries ago with variolation, the practice of inoculating fluid from smallpox lesions into skin of susceptible persons. Although this technique usually produced mild illness without complications, spread of disease did occur, with occasional complications. In 1796, Jenner demonstrated that milkmaids who had contracted cowpox (vaccinia) were immune to smallpox. He inoculated the vesicular fluid from cowpox lesions into the skin of susceptible people and induced protection against smallpox, thus beginning the era of immunization.

Immunization, the act of artificially inducing immunity or providing protection from disease, can be active or passive. Active immunization consists of inducing the body to develop defenses against disease. This usually is accomplished by means of administration of vaccines or toxoids that stimulate the body's immune system to produce antibodies or cell-mediated immunity, or both, which protects against the infectious agent.[2] Passive immunization consists of providing temporary protection through administration of exogenously produced antibody. Two situations in which passive immunization commonly occurs are through transplacental transfer of antibodies to the fetus, which may provide protection against certain diseases for the first 3 to 6 months of life, and injection of immunoglobulins for specific preventive purposes. A more detailed description of the immune mechanisms involved follows.

Immunizing agents include vaccines, toxoids, and antibody-containing preparations from human or animal donors. Several important definitions are provided here.

1. *Vaccine:* a suspension of attenuated, live, or killed microorganisms (bacteria, viruses, or rickettsiae), or fractions thereof, that is administered to induce immunity and thereby prevent infectious disease.
2. *Toxoid:* a modified bacterial toxin that has been rendered nontoxic but retains the ability to stimulate formation of antitoxin.
3. Immunoglobulin products include standard immune globulin (IG) for intramuscular (IM) use, hyperimmune globulins that are available for IM and/or intravenous (IV) use, standard immune globulin intravenous (IGIV), immune globulin subcutaneous (IGSC), antibodies of animal origin, and monoclonal antibodies. IG is a sterile, concentrated protein solution containing antibodies from human blood that reflect the infectious and immunization experience of the population from whose plasma the IG was prepared. IG contains 15% to 18% protein, consisting primarily of the immunoglobulin G (IgG) fraction (90%) with trace amounts of immunoglobulin A (IgA) and immunoglobulin M (IgM). IG primarily is indicated for routine protection of certain immunodeficient persons and for passive immunization against measles and hepatitis A. IGIV is indicated primarily for replacement therapy in immunoglobulin G (IgG) deficiency and pediatric human immunodeficiency virus (HIV) infection, treatment of Kawasaki disease, and idiopathic thrombocytopenic purpura. IGSC is indicated primarily for treatment of antibody deficiency.
4. Specific immunoglobulin: special preparations are obtained from donor pools preselected for high antibody content against a specific disease—for example, hepatitis B immune globulin (HBIG), varicella-zoster immune globulin (VariZIG), rabies immune globulin (RIG), tetanus immune globulin (TIG), and botulism IGIV used to treat infant botulism.

The constituents of immunizing agents include the following:

1. *Suspending fluid:* This frequently is as simple as sterile water or saline, but it may be a complex fluid containing small amounts of proteins or other constituents derived from the medium or biologic system in which the immunizing agent is produced (serum proteins, egg antigens, cell culture–derived antigens).
2. *Preservatives, stabilizers, antibiotics:* These components of vaccines are used (1) to inhibit or prevent bacterial growth in viral culture or the final product (preservatives and antimicrobial agents) or (2) to stabilize the antigen against changes in temperature and/or pH (stabilizers). They include materials such as mercurials (thimerosal), gelatin, and specific antimicrobial agents. Allergic reactions may occur if the recipient is sensitive to any of these additives. Preservatives are required for multidose vaccine formulations or vials to prevent bacterial or fungal growth, should they be introduced on repeated entry into the vial. Thimerosal, an ethylmercury-containing preservative, has been the major preservative used in vaccines around the world. A review of the mercury content of vaccines in the United States in 1999 indicated that some children had received quantities of ethylmercury from thimerosal in excess of some federal guidelines for methyl mercury. As a precautionary measure, thimerosal as a preservative was removed from most vaccines in the immunization schedule to the extent feasible.[3] However, some of these vaccines may contain trace amounts (www.fda.gov/cber/vaccine/thimerosal.htm). Subsequent studies of potential adverse consequences of thimerosal have not demonstrated significant harm from its use in vaccines. It is likely had these data been available in 1999, the United States would not have made the decision to remove thimerosal from vaccines for children.[4,5] Some vaccines for children contain other preservatives (e.g., 2-phenoxyethanol) or do not need a preservative because they are packaged in single-dose vials. Influenza vaccines in multidose vials used in adults and combined adult-type tetanus and diphtheria toxoids (Td) contain thimerosal as a preservative.[6]
3. *Adjuvants:* An aluminum salt is used in some vaccines to enhance the immune response to vaccines containing inactivated microorganisms or their products (e.g., toxoids and hepatitis B vaccine). Bivalent human papillomavirus vaccine contains an aluminum salt combined with monophosphoryl lipid A. An oil-in-water adjuvant is used in one influenza vaccine licensed in the United States and in other vaccines licensed outside the United States. Recombinant zoster vaccine (RZV) contains monophosphoryl lipid A combined with saponin. Vaccines with such adjuvants should be injected deeply into muscle masses

because subcutaneous or intracutaneous administration can cause local irritation, inflammation, granuloma formation, or necrosis.[7]

IMMUNOLOGIC BASIS OF VACCINATION

Two major approaches to active immunization have been used: use of live (attenuated) infectious agents, and use of inactivated, or detoxified, agents or their extracts. For many diseases (including influenza, poliomyelitis, typhoid, and measles), both approaches have been used. Live-attenuated vaccines are believed to induce an immunologic response more similar to that resulting from natural infection than do killed vaccines. Inactivated or killed vaccines can consist of inactivated whole organisms (e.g., hepatitis A vaccine), detoxified exotoxin (e.g., diphtheria and tetanus toxoids), soluble capsular material either alone (e.g., pneumococcal polysaccharide), or covalently linked to carrier protein (e.g., *Haemophilus influenzae* type b [Hib] conjugate vaccines), chemically purified components of the organism (e.g., acellular pertussis, inactivated influenza vaccines [IIVs]), or recombinant proteins (e.g., hepatitis B virus [HBV], serogroup B meningococcal vaccine [MenB-FHbp/MenB-4C], virus-like particles [VLPs; e.g., human papillomavirus (HPV)], or RZV).

Determinants of Immunogenicity

The immune system is complex, and antigen composition and presentation are critical for stimulation of the desired immune response. Immunogenicity is determined not only by the chemical and physical states of the antigen but also by the genetic characteristics of the responding individual, the physiologic condition of the individual (e.g., age, nutrition, sex, pregnancy status, stress, infections, immune status), and the manner in which the antigen is presented (route of administration, dose or doses and timing of doses, and presence of adjuvants).[8,9]

Live Versus Killed or Subunit Vaccines

Because the organisms in live vaccines multiply in the recipient, antigen production increases logarithmically until controlled by the immune response induced by the antigen. The live-attenuated viruses (e.g., measles, rubella) generally are believed to confer lifelong protection in those who respond. By contrast, killed vaccines (e.g., diphtheria, tetanus, rabies, typhoid) generally do not induce permanent immunity with one dose, requiring repeated vaccination and subsequent boosters for development and maintenance of high levels of antibody. Exceptions to this general rule may include hepatitis B vaccine, for which long-term immunologic memory has been demonstrated for approximately 30 years after vaccination[10], and inactivated polio vaccine (IPV), for which the duration of immunity is unknown. Although the amount of antigen initially introduced is greater with inactivated vaccines, multiplication of organisms in the host results in a cumulatively greater antigenic input with live vaccines.

Most vaccines include protein antigens, which generate a T-lymphocyte–dependent immune response. This response induces immunologic memory, booster effects with repeat administration, and good immunogenicity in all age groups. However, purified bacterial capsular polysaccharide vaccines induce a T-lymphocyte–independent immune response, which does not lead to immune memory and cannot be boosted with repeated injections.[11] Polysaccharide vaccines have poor immunogenicity in infants and young children. Covalent linkage of the polysaccharide to a carrier protein converts it from a T-lymphocyte–independent to a T-lymphocyte–dependent antigen (e.g., conjugated Hib, pneumococcal, and meningococcal vaccines), which produces a good immune response in infants and children.

Dose

The amount of antigen determines the immune response. Presentation of an insufficient amount of antigen may result in no immune responsiveness. There is usually a dose-response curve relationship between antigen dose and peak response obtained beyond a threshold; however, responsiveness may reach a plateau, failing to increase beyond a certain level despite increasing doses of vaccine.

Adjuvants

The immune response to some inactivated vaccines or toxoids can be enhanced by addition of adjuvants, such as aluminum salts (either alone or in combination with monophosphoryl lipid A).[11a] Adjuvants are particularly useful with inactivated products, such as diphtheria and tetanus toxoids, acellular pertussis vaccines (DTaP), and hepatitis B vaccine. The mechanism of enhancement of antigenicity by adjuvants is not well defined; however, it is increasingly clear that adjuvants activate the innate immune system through pathogen-associated molecular patterns (PAMPs). Licensed adjuvants for use in humans in the United States include aluminum salts alone or with monophosphoryl lipid A, squalene-based oil-in-water emulsion, and synthetic oligodeoxynucleotides.[12]

Route of Administration

The route of administration can determine the nature of the immune response to a vaccine or toxoid. IM or subcutaneous delivery results in a predominantly IgG response. Oral (e.g., rotavirus vaccine and typhoid vaccine Ty21a) or nasal (e.g., live-attenuated influenza vaccine [LAIV]) vaccination is more likely to result in production of local IgA compared with IM injection, although systemic IgG also is induced. The immunogenicity of some vaccines is reduced when not given by the recommended route. For example, administration of hepatitis B vaccine subcutaneously into the fatty tissue of the buttock was associated with substantially lower seroconversion rates than injection intramuscularly into the deltoid muscle.[13]

Most vaccines are administered either intramuscularly or subcutaneously.

Age

The immune response to a vaccine varies with age. Although children and young adults usually respond well to all vaccines, differences in response capability exist during early infancy and older age. The presence of high levels of passively acquired maternal antibody in the first few months of life impairs the initial immune response to some killed vaccines (e.g., hepatitis A vaccine,[14] diphtheria toxoid) and many live vaccines (e.g., measles). Prematurely born infants of low birth weight should be immunized at the usual chronologic age in most cases. Infants with birth weights less than 2000 g may require modification of the timing of hepatitis B immunoprophylaxis, depending on maternal hepatitis B surface antigen (HBsAg) status.[15] Some studies have suggested a reduced immune response in very-low-birth-weight infants (<1500 g) immunized according to the usual schedule; however, antibody concentrations achieved usually are protective. In older adults, the response to antigenic stimulation may be diminished (e.g., influenza, hepatitis B vaccines). This has led to the development of higher-potency influenza vaccines for use in the elderly.

COMPONENTS OF THE IMMUNE RESPONSE

The immune response traditionally is divided into two components: the innate immune response, which is rapid, nonspecific, and serves as an immediate first line of defense against an infection, and the adaptive immune response, which develops over a matter of days, is specific for the foreign antigen, and results in long-term immune memory. The latter protects the host against subsequent challenge with the same or immunologically similar pathogens and is the underlying principle of vaccination. The innate immune response is mediated by natural killer (NK) cells, which recognize and kill virally infected cells; by complement, which is activated by components of bacterial cell walls; and by phagocytes, including macrophages and dendritic cells (DCs), which ingest microorganisms and foreign particulates.[16] The adaptive immune response relies on antigen-presenting cells (APCs), such as DCs, for activation and is mediated by T and B lymphocytes. T lymphocytes can be divided into CD4 (helper) and CD8 (cytotoxic) lymphocytes and are responsible for cell-mediated immune responses. CD4 helper T lymphocytes can be further subdivided into Th1 lymphocytes, which predominantly lead to cell-mediated responses, and Th2 lymphocytes, which predominantly lead to humoral responses. B lymphocytes produce antibody specific for the immunizing agent and require CD4–T-lymphocyte help. Interactions between APCs, helper T-lymphocytes, and B-lymphocytes involve class II major histocompatibility complex (MHC) antigens, whereas interactions between cytotoxic T lymphocytes and their target involve MHC class I antigens.[17] Soluble mediators or cytokines are secreted by

all cell types and serve as activation and differentiation factors for different cell lineages. These include interleukins, interferons, and others.[18] A further class of CD4 T lymphocytes (Treg) plays an essential role in the regulation of the adaptive immune response.[19]

The innate immune response is able to respond differently to different types of pathogens, and these differential responses help determine the nature of the subsequent adaptive response.[20] Pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs), nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), and others, encoded in the germline recognize PAMPs and contribute to immune activation by inducing proinflammatory cytokines, which in turn modulate the adaptive immune response. As alluded to earlier, this has significant implications for adjuvant development.[21,22]

MOBILIZATION OF THE ADAPTIVE IMMUNE RESPONSE

On exposure to an infectious organism or a vaccine, the innate immune system is mobilized through APC recognition of PAMPs that are present either in the organism or in the adjuvant. Activated APCs (macrophages and DCs) secrete proinflammatory cytokines and chemokines, which recruit other leukocytes to the site of infection. When activated, DCs migrate to the draining lymph nodes, where they interact with T lymphocytes through the MHC-peptide complex.[23] Once the organism or antigen is internalized, it is killed and broken down into peptides. These peptides are transported to the cell surface through membrane trafficking and bind to MHC class I or class II molecules. MHC class I molecules are able to bind peptides that are 8 to 10 amino acids in length, whereas MHC class II molecules are more permissive, binding peptides of 13 amino acids and greater.[24]

The first step in the induction of a T-lymphocyte–dependent antibody response is the activation of naïve CD4 helper T lymphocytes by presentation of an antigen by phagocytes or DCs. The T-lymphocyte receptor recognizes the MHC-peptide complex, and this recognition triggers secretion of cytokines, which stimulate maturation of naïve helper T lymphocytes. In the presence of interleukin-12 (IL-12), Th1 lymphocytes will differentiate, and these in turn will secrete IL-2 and interferon-γ. In the presence of IL-4, Th2 lymphocytes will differentiate and secrete IL-4 and IL-5. These two cytokines are essential for the differentiation and maturation of B lymphocytes into antibody-secreting plasma cells.

Naïve B lymphocytes recognize a specific antigenic epitope on native antigen through the immunoglobulin receptor on their surface but are unable to differentiate into antibody-secreting lymphocytes without T-lymphocyte help. A given B lymphocyte can be activated only by a T lymphocyte responding to the same antigen, though not necessarily to the same epitope. A helper T lymphocyte will recognize the MHC class II complex on the surface of the B lymphocyte and deliver a signal for B-lymphocyte differentiation. This leads to B-lymphocyte proliferation and maturation in a clonal manner. Class switching (from IgM to IgG and IgA) and affinity maturation occur, and antigen-specific plasma cells develop. However, not all B lymphocytes become plasma cells. Some mature into memory B cells, which are long-lived and form the basis of the rapid secondary response on the next encounter with the pathogen.[25] Although the mechanism of maintenance of these cells is not clear, the ability to mount a strong secondary response after many years argues for a homeostatic mechanism that regulates these cells. The antibodies formed after vaccination express a variety of antigen-binding specificities (i.e., recognize different structures on a complex multideterminant antigen), reflecting the sum of the large number of individual clonal B-lymphocyte responses that make up an antibody response.

Antibodies mediate protection through a variety of mechanisms. They may inactivate soluble toxic protein products of bacteria (antitoxins), facilitate intracellular digestion of bacteria by phagocytes (opsonization), interact with components of serum complement to damage the bacterial membrane with resultant bacteriolysis (lysins), prevent infectious virus from infecting cells (neutralizing antibodies), or interact with components of the bacterial surface to prevent adhesion to mucosal surfaces (anti-adhesins). Antibodies cannot readily reach intracellular sites of infection, the sites of viral and some bacterial replication. However, antibodies are effective against many viral diseases through interaction with viruses before initial intracellular penetration occurs and through prevention of locally replicating viruses from disseminating from the site of entry to an important target organ, as in the spread of poliovirus from the intestine to the central nervous system or rabies from a puncture wound to peripheral neural tissue.

Virally infected cells can be killed by cytotoxic CD8 T lymphocytes. As the virus replicates in a cell, viral proteins are processed and presented on the cell surface as an MHC class I–peptide complex, which is then recognized by cytotoxic T lymphocytes. Cells infected with intracellular bacteria, such as *Mycobacterium leprae,* are recognized and killed in the same way.

UNANTICIPATED RESPONSES

Independent of antibody production, stimulation of the immune system by vaccination may, on occasion, elicit a hypersensitivity response. Killed measles vaccine, used in the United States between 1963 and 1967, induced incomplete humoral immunity and cell-mediated hypersensitivity, resulting in development of a syndrome of atypical measles in some children on subsequent exposure to measles.[26] In addition, some antibodies produced may not be protective but block the reaction of protective antibodies with antigens, inhibiting the body's defenses. Some vaccines may induce immunologic tolerance that results in blunting of the immune response on subsequent exposure to the antigen (e.g., meningococcal polysaccharide vaccine [MPSV]).[27] Concerns have been raised that immunizations might induce autoimmune disorders. However, careful reviews of both the possible biologic mechanisms and epidemiologic evidence generally have failed to confirm vaccines as causes of these disorders.[28] The evidence was insufficient to accept or reject a causal relationship between vaccines and allergic disorders, particularly asthma.[29] A subsequent epidemiologic study failed to show an association between vaccines and asthma.[30] Concerns also have been raised that the number of antigens in the current vaccine schedule might overwhelm an infant's immune system, leading to chronic diseases and predisposing to other serious infections.[31] As a result of removal of whole-cell pertussis vaccine and smallpox vaccine from the current immunization schedule, the number of immunogenic proteins and polysaccharides a child is exposed to today is actually smaller than in the past. Estimates suggest that an infant is capable of responding to 10,000 vaccine antigens simultaneously.[32] The Institute of Medicine (IOM) concluded that available evidence favored rejection of a causal relationship between vaccines and increased risk for infections. IOM also concluded that available evidence favored rejection of a causal relationship between vaccines and type 1 diabetes mellitus.[29]

TEMPORAL COURSE OF THE IMMUNE RESPONSE

On first exposure to a vaccine, a primary response is induced, and a protective immune response will develop in about 2 weeks. Circulating antibodies do not usually appear for 7 to 10 days, and the immunoglobulin class of the response changes over this period of time. Early-appearing antibodies are usually of the IgM class and of low affinity; late-appearing antibodies are usually of the IgG class and display a high affinity. IgM antibodies may fix complement, making lysis and phagocytosis possible. As the titer of IgG rises during the second week (or later) after immunogenic stimulation, the IgM titer falls. IgG antibodies are produced in large amounts and function in the neutralization, precipitation, and fixation of complement. The antibody titer frequently reaches a peak in about 2 to 6 weeks and then falls gradually. The switch from IgM synthesis to predominantly IgG synthesis in B lymphocytes is mediated by T-lymphocyte help. Uncommonly, people may not respond to a vaccine, experiencing a primary vaccine failure. This may be due to a genetic inability to respond to vaccine, but other factors are involved. For example, almost all children who do not respond immunologically to the first dose of measles-mumps-rubella (MMR) vaccine will acquire measles immunity after a second dose.[32]

After a second exposure to the same antigen, a heightened humoral or cell-mediated response, an anamnestic response, is observed. These secondary responses occur sooner than the primary response, usually within 4 to 5 days, and depend on a marked proliferation of antibody-producing cells or effector T lymphocytes. Effector T lymphocytes, also

known as memory T cells, are T lymphocytes that have a memory of a previous immune response. The secondary response depends on immunologic memory after the first exposure mediated by both T and B lymphocytes. Infection with measles or varicella vaccine strains has been shown to evoke a cell-mediated in addition to a humoral response.

Many pathogens replicate at mucosal surfaces before host invasion and may induce secretory IgA along the respiratory and gastrointestinal mucous membranes and at other localized sites (e.g., polio, rubella, influenza, rotavirus). IgA antibodies are efficient at virus neutralization (e.g., polio), fix complement through the alternative pathway (e.g., cholera), prevent adsorption of organisms to the intestinal wall (e.g., *Escherichia coli,* cholera), and can lyse gram-negative bacteria (with the aid of both complement and lysozyme).[34] Current parenteral, especially inactivated, vaccines rarely induce high levels of secretory IgA antibodies.

MEASUREMENT OF THE IMMUNE RESPONSE

Response to vaccines is often gauged by measuring the appearance and concentration of specific serum antibodies.[35] For some viral vaccines, such as those for measles and rubella, the presence of circulating antibodies correlates with clinical protection. Although this has served as a dependable indicator of immunity, seroconversion measures only the humoral parameter of the immune response. Secondary vaccine failure occurs when an individual who previously had developed an adequate immune response loses protection over time. This waning immunity can be attributed to a loss of long-lived memory B or T cells in the absence of repeated exposure to the pathogen. Evaluating persistence of antibody has been used to determine the duration of vaccine-induced immunity for those diseases for which antibody is judged to be a good correlate of protection. However, the absence of measurable antibody may not mean that the individual is unprotected. Although a fall in titer occurs, on revaccination or challenge a rapid secondary response is observed in IgG antibodies, with little or no detectable IgM response, suggesting persistent protection. With some vaccines and toxoids, the mere presence of antibodies is not sufficient to ensure clinical protection, but rather a minimal circulating level of antibody is required (e.g., 0.01 IU/mL of tetanus antitoxin). Functional antibody is important in assessing immunity to bacterial polysaccharide vaccines. Opsonophagocytic activity is considered the assay of choice for monitoring vaccine response[36] because the vaccines also induce nonfunctional antibodies that are detected in standard enzyme immunosorbent assay (EIA), although the EIA can be used as a proxy. Some immune responses may not in themselves confer immunity but may be sufficiently associated with protection that they remain useful proxy measures of protective immunity (e.g., vibriocidal serum antibodies in cholera). The measurement of cell-mediated immunity, which would be helpful in assessing the degree of ongoing protection in many circumstances, usually is limited to research laboratories and to only a few vaccines.

VACCINE DEVELOPMENT

Most vaccines in use today have been developed by empirical techniques.[37] For live-attenuated viral vaccines, organisms are repeatedly passaged in various tissue culture cell lines to reduce virulent properties while maintaining immunogenicity. Inactivated vaccines usually have been developed by growing microorganisms, followed by concentration, purification, and inactivation, not necessarily in that order. Component vaccines usually are derived from chemical separation of the needed component from the parent organism.

Future vaccines are likely to be derived from new methods of biotechnology, especially recombinant techniques. Currently available hepatitis B vaccines were developed by cloning the HBsAg gene into yeast, leading to synthesis of HBsAg within the yeast cell. Other new approaches for producing vaccines include live vectors, in which one or more genes encoding critical determinants of immunity from pathogenic microorganisms are inserted into the genome of the vector, followed by the administration of the vector as a component of the vaccine. These vectors may include viruses, such as poxviruses (vaccinia or canarypox), or bacteria, such as *Salmonella* or bacillus Calmette-Guérin (BCG). Additional newer techniques include microencapsulation of critical antigens in polymers, which can lead to sustained release or pulse release over prolonged periods, mimicking the effect of multiple injections of an antigen over a several-month interval. New technologies also include use of nucleic acids, which encode critical antigens. Injection of the DNA, combined with administration of a protein at a later point in time, leads to production of antigen without risk for producing whole infectious organisms. LAIV was developed using genetic reassortment of the genes encoding two of the surface glycoproteins from wild virus isolates with six other genes contributed from a cold-adapted, temperature-sensitive influenza strain. Similar techniques were used to develop bovine rotavirus vaccines.[38] Last, newer technologies focus on the development of adjuvants to help stimulate the immune response.[39]

General Principles of Immunization

Introduction and widespread use of vaccines resulted in global eradication of smallpox, elimination of poliomyelitis caused by wild viruses in the United States and most of the countries of the world, and dramatic reductions in the incidence rates of other diseases (Tables 316.1 and 316.2). Measles and rubella are no longer considered endemic in the Americas.[40,41] Measles and rubella have been reduced by greater than 90% in developed countries and, if global vaccination efforts can be sustained, may eventually be eliminated from many countries. The World Health Assembly had established a goal to eradicate polio from the world by the end of 2000.[42] Although that goal was not achieved, by the end of 2016 only three countries in the world had never interrupted wild poliovirus transmission (www.polioeradication.org).[43] The last case of polio caused by wild virus in the Western Hemisphere was in 1991; four of the six regions of the World Health Organization (WHO)—American, European, Southeast Asian, and Western Pacific—have been certified free of wild poliovirus.[44–46] Global use of hepatitis B vaccine in infants may have an impact comparable to that of other vaccines in childhood. Hib vaccines have only recently come into widespread use, but disease incidence has been reduced markedly in many developed countries.[47–50] Reductions based on historical estimates have been achieved for congenital rubella syndrome and Hib invasive disease.[51] Despite these successes, cases of measles and pertussis continue to occur in the United States (see Table 316.1). All measles cases are the result of

TABLE 316.1 Representative 20th-Century Morbidity Cases in 2017 and Change

DISEASE	20th CENTURY ANNUAL MORBIDITY[a]	2017 REPORTED CASES[b]	PERCENT DECREASE
Smallpox	29,005	0	100%
Diphtheria	21,053	0	100%
Measles	530,217	120	>99%
Mumps	162,344	6109	96%
Pertussis	200,752	18,975	91%
Polio (paralytic)	16,316	0	100%
Rubella	47,745	7	>99%
Congenital rubella syndrome	152	5	99%
Tetanus	580	33	94%
Haemophilus influenzae	20,000	33[c]	>99%

[a]From Roush SW, Murphy TV; Vaccine-Preventable Disease Table Working Group. Historical comparisons of morbidity and mortality for vaccine-preventable diseases in the United States. *JAMA*. 2007;298;2155–2163.
[b]Centers for Diease Control and Prevention. *National Notifiable Diseases Surveillance System, 2017 Annual Tables of Infectious Disease Data.* Atlanta: CDC Division of Health Informatics and Surveillance; 2018.
[c]*H. influenzae* type b (Hib) at <5 years of age. An additional 10 cases of Hib are estimated to have occurred among the 203 notifications of *H. influenzae* (<5 years of age) with unknown serotype.

TABLE 316.2 Representative 20th-Century Morbidity Cases in 2016 and Change

DISEASE	PREVACCINE ERA ANNUAL ESTIMATE	2016 ESTIMATE (UNLESS OTHERWISE SPECIFIED)	PERCENT DECREASE
Hepatitis A	117,333[a]	4000[b]	97%
Hepatitis B (acute)	66,232[a]	20,900[b]	68%
Pneumococcus (invasive)			
All ages	63,067[a]	30,400[c]	52%
<5 yr of age	16,069[a]	1700[c]	89%
Rotavirus (hospitalizations, <3 yr of age)	62,500[d]	30,625[e]	51%
Varicella	4,085,120[a]	102,128[f]	98%

[a]Rousch SW, Murphy TV; Vaccine-Prevenatable Disease Table Working Group. Historical comparisons of morbidity and mortality for vaccine-preventable diseases in the United States. *JAMA.* 2007;298:2155–2163.
[b]Centers for Disease Control and Prevention. Viral hepatitis surveillance—United States, 2016.
[c]Centers for Disease Control and Prevention. Active bacterial core surveillance 2016 (unpublished).
[d]Cortese MM, Parashar UD; Centers for Disease Control and Prevention. 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.
[e]New Vaccine Surveillance Network 2017 data (unpublished); US rotavirus disease now has a biennial pattern.
[f]Centers for Disease Control and Prevention. Varicella Program 2017 data (unpublished).

international importations, some of which spread within the US population, whereas pertussis remains endemic.

Pneumococcal conjugate vaccines (PCVs) have had a marked impact on invasive pneumococcal disease in countries where they have been used widely in children.[52,53] Decreases in disease were observed not only in children but also in adults, who presumably are not being exposed to infectious children because the latter have had vaccine-type pneumococcal carriage eliminated by vaccination.

Modern vaccines are safe and generally effective. Each vaccine is associated with some adverse effects, which are usually mild, and only rarely life-threatening. No vaccine is 100% effective. Consequently, some persons who have received a complete vaccine or toxoid series may acquire disease after exposure. The effectiveness of vaccines recommended for universal use in children is well defined, with most vaccines protecting more than 80% of recipients after a primary series.

In most studies, acellular pertussis vaccines range in efficacy from 63% to 99% during the first few years after vaccination.[54,55,56] One dose of varicella vaccine is 95% or more effective against severe varicella but is less effective against varicella of any severity.[57,58] With some vaccines, antibody may wane, but immunologic memory is sufficient to prevent disease if the individual is exposed (e.g., hepatitis B).[59] However, for some diseases with short incubation periods (e.g., meningococcal disease), waning antibody after vaccination is associated with waning protection. This waning has occurred with meningococcal conjugate vaccines, resulting in the need for modification of the originally recommended vaccine schedule with the addition of a second dose.[60] Another example of loss of durability has occurred with the Tdap (tetanus, diphtheria, and acellular pertussis) and DTaP (diphtheria and tetanus toxoids and acellular pertussis) vaccines, in which protection begins to wane a few years after administration.[61–63]

Although high efficacy of each of these vaccines is apparent, there has been substantial controversy about reported adverse events temporally associated with vaccination. Because of these controversies, the IOM reviewed available information, and between 1991 and 2013 published multiple reports.[64–67] In the 1991 and 1994 studies, the IOM found insufficient evidence to indicate a causal relationship between DTaP and permanent neurologic damage, and the IOM favored rejection of a causal relationship between combined diphtheria and tetanus toxoids (DT) and encephalopathy and between conjugate Hib vaccines and early-onset Hib disease. The IOM also concluded that the evidence establishes a causal relationship between MMR and thrombocytopenia, between rubella vaccine and acute arthritis, between DT and brachial neuritis, and between a variety of vaccines and anaphylaxis. In 2004 the IOM reported the relationships between a variety of disorders and vaccines (www.iom.edu/Activities/PublicHealth/ImmunizationSafety.aspx).[67,68] The IOM panel concluded that evidence did not support a relationship between MMR or thimerosal and autism, between multiple immunizations and heterologous infections, between multiple immunizations and type 1 diabetes, or between hepatitis B vaccine and incident or relapsed multiple sclerosis. In 2011 the IOM looked at the relationship of vaccines with many conditions that are reported after vaccination and, in most cases, found no evidence to support such associations. The IOM specifically found evidence to support rejection of an association between MMR vaccine and autism. Likewise, it found evidence to reject an association between IIV and asthma. In 2013 the IOM studied the impact of giving multiple vaccines to an individual in accordance with Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC), American Academy of Pediatrics (AAP), and American Academy of Family Physicians (AAFP) recommendations and found no evidence of a safety concern with adhering to the childhood schedule.[69]

Development of vaccines consists of four phases. Initial studies typically are conducted in animal models to demonstrate protection (or at least production of antibodies) and relative safety. These are called *preclinical studies.* Then limited numbers of doses are administered to humans to demonstrate antibody production and safety (phase I). After this phase, clinical trials in humans are conducted in a limited number of people to select optimal vaccine schedules and to demonstrate further safety (phase II). Larger trials are conducted to demonstrate efficacy (phase III). Because of their limited size, these field trials can be expected to detect adverse events that occur only relatively frequently (1 per 1000 doses or higher). After clinical trials, licensure may be sought. In the United States, vaccine production is regulated by the Center for Biologics Evaluation and Research (CBER) of the US Food and Drug Administration (FDA). Only after a vaccine has been found to be safe and effective is it licensed for use. Postmarketing surveillance (phase IV) is necessary to detect rare adverse events associated with vaccination and to monitor safety of vaccination practices, such as simultaneous immunization.

There is no direct evidence of risk to the fetus when pregnant women are given vaccines routinely recommended during pregnancy by ACIP. The benefit of IIV to the pregnant mother and the fetus outweighs any risk of vaccination to the mother or the fetus.[70] Some vaccines are recommended for pregnant women in order to provide passive immunity to their fetuses so that when the child is born, the child is protected before active immunity can be induced through direct vaccination of the infant. Thus, Tdap and nonlive influenza vaccine is recommended during each pregnancy.[6,70,71] Most live-virus vaccines induce viremia, which at least theoretically could result in infection of the fetus, so live-virus vaccines are not administered to pregnant women except in unusual circumstances, when potential benefit clearly outweighs the risk.

The decision to administer a vaccine involves assessment of risks of disease, benefits of vaccination, and risks associated with vaccination. The relative balance of risks and benefits may change over time; consequently, continuing assessment of vaccines is essential. Recommendations for vaccine use are developed by several different bodies: ACIP develops recommendations for vaccines for children, adolescents, and adults in the civilian population in conjunction with professional societies. These recommendations are updated annually and are available at www.cdc.gov/vaccines/schedules/hcp/index.html. Since 2011, the ACIP process for making vaccine recommendations has included a careful evaluation of the strength of the evidence supporting recommendations, which is known as GRADE (Grading of Recommendations, Assessment, Development and Evaluation; www.cdc.gov/vaccines/acip/recs/GRADE/

table-refs.html). The Committee on Infectious Diseases (COID) of the AAP (the "Red Book " committee) develops recommendations for vaccine use in infants, children, and adolescents.[72] Since 1995, ACIP, the AAP, and the AAFP have collaborated to issue a harmonized childhood immunization schedule, which is updated annually. The childhood immunization schedule consists of three parts: one based on age, a second that is a catch-up schedule for children who are behind on their immunizations, and a third that is based on underlying medical conditions (Fig. 316.1).[73] ACIP also annually issues an adult immunization schedule in two parts: (1) recommendations based on age group and (2) recommendations based on underlying medical conditions (Figs. 316.2 to 316.4), which can be found at www.cdc.gov/vaccines/schedules/hcp/adult.html. The Adult Immunization Schedule for 2018 was harmonized with the AAFP, the American College of Obstetricians and Gynecologists, the American College of Physicians, and the American College of Nurse-Midwives.

CURRENTLY AVAILABLE IMMUNIZING AGENTS

Tables 316.3 and 316.4 list currently licensed immunizing agents and immunoglobulins. This section presents brief information about most immunizing agents, primary indications for use, relative efficacy, number and spacing of doses required, known adverse effects, and precautions and contraindications for use. Package inserts and specific references and recommendations should be consulted for more detailed information. In addition to these licensed products, several other vaccines are under development and may become available.

Vaccines

Adenovirus Vaccine

Adenovirus vaccine contains live adenovirus types 4 and 7. It is recommended only for military personnel who are 17 through 50 years of age. It is taken as two oral tablets (one dose). Serious adverse events possibly associated with receipt of vaccine included hematuria, gastroenteritis, gastritis, pneumonia, and hematochezia.

Anthrax Vaccine

Anthrax vaccine (AVA) is prepared from microaerophilic cultures of an avirulent nonencapsulated strain of *Bacillus anthracis*. The vaccine is a cell-free filtrate that contains a mixture of components, including protective antigen (the antigen that is thought to confer immunity) and other bacterial products adsorbed to aluminum hydroxide. Because of concerns about potential use of *B. anthracis* as a biologic warfare agent, vaccination of selected members of the US Armed Forces was begun in 1998. After the intentional release of anthrax in the United States in 2001, anthrax vaccine was recommended for civilians at risk for repeated exposure to *B. anthracis* spores, including laboratory personnel handling environmental specimens and performing confirmatory testing for *B. anthracis* in selected laboratories and workers making repeated entries into sites known to be contaminated with *B. anthracis* spores. Anthrax vaccine also was used after exposure, in conjunction with antimicrobial prophylaxis, under an investigational protocol.[74] Groups for whom preexposure vaccination is recommended include persons working with production quantities of *B. anthracis* cultures or in activities with a high potential for aerosol production and selected other workers at high risk for exposure to *B. anthracis* spores.[75] Efficacy has been demonstrated in protection against cutaneous disease. Data on clinical efficacy against inhaled anthrax in humans are limited, but available human and animal data are consistent with protection.[76] The vaccine induces antibodies in greater than 90% of adults who received the currently recommended primary course of three IM injections given at time zero, 4 weeks, and 6 months, with boosters at 12 months and 18 months, followed by annual boosters.[75,77] A controlled study of a vaccine similar to the currently available vaccine demonstrated protective efficacy against cutaneous disease of 93% among mill workers.[78] Experience suggests that two doses of vaccine confer some protection.[79] Mild

TABLE 316.3 Currently Available Vaccines and Toxoids and Year Licensed

PRODUCT	YEAR LICENSED
Adenovirus vaccine, live, attenuated	2014
Anthrax vaccine adsorbed	1972
Calmette-Guérin bacillus vaccine; live, attenuated	1950
Cholera vaccine, live, attenuated	2016
Dengue tetravalent vaccine, live	2019
Diphtheria and tetanus toxoids and acellular pertussis vaccine	1991
Diphtheria and tetanus toxoids adsorbed (pediatric use, DT)	1949
Diphtheria and tetanus toxoids and acellular pertussis vaccine absorbed, *Haemophilus* B conjugate vaccine, and inactivated polio vaccine combined	2008
Diphtheria and tetanus toxoids and acellular pertussis vaccine absorbed and inactivated polio vaccine combined	2008
Diphtheria and tetanus toxoids and acellular pertussis adsorbed, hepatitis B (recombinant), and inactivated poliovirus vaccine combined	2002
Haemophilus influenzae type b conjugate vaccine	1987
Hepatitis A vaccine	1995
Hepatitis A inactivated and hepatitis B (recombinant) vaccine	2001
Hepatitis B recombinant vaccine	1987
Human papillomavirus vaccine	2006
Influenza virus vaccine (cell culture)	2013
Influenza virus vaccine (inactivated)	1945
Influenza virus vaccine; live, attenuated, intranasal	2003
Influenza virus vaccine; recombinant hemagglutinin	2014
Japanese encephalitis vaccine	2009
Measles virus vaccine; live, attenuated	1963
Measles, mumps, rubella, varicella; live, attenuated	2005
Measles, mumps, and rubella virus vaccine; live, attenuated	1971

TABLE 316.3 Currently Available Vaccines and Toxoids and Year Licensed[a]—cont'd

PRODUCT	YEAR LICENSED
Meningococcal polysaccharide (serogroups A, C, Y, and W) conjugated to diphtheria toxoid	2005
Pneumococcal conjugate vaccine (13-valent)	2010
Pneumococcal polysaccharide vaccine (23-valent)	1983
Poliomyelitis vaccine (inactivated, enhanced potency)	1987
Rabies vaccine (human diploid)	1980
Recombinant zoster vaccine	2017
Rotavirus vaccine, live, attenuated	2006
Rubella virus vaccine, live, attenuated	1969
Serogroup B meningococcal vaccine	2014
Smallpox vaccine, live, attenuated	2007
Tetanus and diphtheria toxoids, adsorbed (adult use, Td)	1955
Tetanus toxoid adsorbed	1949
Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine, absorbed	2005
Typhoid vaccine (polysaccharide)	1994
Typhoid vaccine; live, attenuated (oral)	1990
Varicella vaccine; live, attenuated	1995
Yellow fever vaccine; live, attenuated	1953
Zoster vaccine; live, attenuated	2006

[a]As of January 2017.

TABLE 316.4 Immune Globulin Preparations Made From Human Plasma[a]

NAME	ABBREVIATION	ROUTE OF ADMINISTRATION	YEAR LICENSED
Anthrax immune globulin		Intravenous	2015
Botulism intravenous immune globulin	BabyBIG	Intravenous	2003
Cytomegalovirus immune globulin intravenous	CMV IGIV	Intravenous	1990
Hepatitis B immune globulin	HBIG	Intramuscular	1977
Immune globulin	IG	Intramuscular	1943
Immune globulin intravenous	IGIV	Intravenous	1981
Immune globulin subcutaneous	IGSC	Subcutaneous	2006
Rabies immune globulin	RIG	Intramuscular	1974
Tetanus immune globulin	TIG	Intramuscular	1957
Vaccinia immune globulin intravenous	VIG-IGIV	Intravenous	2005
Varicella-zoster immune globulin	VariZIG	Intramuscular	2012[c]

[a]Antitoxin preparations from animal sera other than humans are available for botulism and diphtheria.
[b]As of January 2017.
[c]A previous preparation of varicella-zoster IG (VZIG) was licensed in 1980.

local reactions at the site of injection occur in about 30% of recipients. Studies of adverse events after injection of the alum-precipitated vaccine, which is the precursor to the AVA vaccine, demonstrate that more severe local reactions occur infrequently (<4%) and systemic reactions are rare (0.2%). Surveillance for adverse events in the military program revealed no pattern of serious adverse events.[80,81] Adverse events, including injection site reaction incidence and duration, were less often seen after IM injection compared with subcutaneous injection.[77] The IM route of administration is indicated for preexposure use.[75] Vaccines containing only recombinant protective antigen are under active development and may be less reactogenic than the current vaccine.[82,83] In the event of exposure to anthrax spores, the recommended postexposure prophylaxis (PEP) regimen is three doses of AVA administered at 0, 2, and 4 weeks, combined with 60 days of antibiotics.[75]

Bacillus Calmette-Guérin Vaccine

BCG vaccine contains living Calmette-Guérin bacillus, an attenuated strain of *Mycobacterium bovis*. In many countries, BCG is used in infants and young children to prevent disseminated tuberculosis infection. In the United States, use of BCG is recommended only in special circumstances because the general risk for infection is low. BCG vaccination can also result in conversion of the purified protein derivative (PPD) or Mantoux tuberculin skin test, thereby removing one of the most important indicators of tuberculosis infection (tuberculin conversion). However, the association of a positive PPD skin test result after immunization with BCG in childhood tends to fade over time, and most individuals will have a PPD reaction of less than 10 mm by 10 years later. BCG does not cross react with the interferon-γ release assay (IGRA), so the IGRA is the preferred test over the PPD for diagnosis of tuberculosis in patients older than 4 years who have received BCG.[84] The IGRA is not as sensitive in children 4 years or younger and requires a blood draw. Although BCG is widely used throughout the world, there has been much controversy regarding its efficacy. Studies have suggested that the vaccine is effective, particularly for preventing complications of disseminated tuberculosis in young children.[85–87] In

Text continued on p. 3785

Table 1 Recommended Child and Adolescent Immunization Schedule for ages 18 years or younger United States, 2019

These recommendations must be read with the Notes that follow. For those who fall behind or start late, provide catch-up vaccination at the earliest opportunity as indicated by the green bars in Table 1. To determine minimum intervals between doses, see the catch-up schedule (Table 2). School entry and adolescent vaccine age groups are shaded in gray.

Vaccine	Birth	1 mo	2 mos	4 mos	6 mos	9 mos	12 mos	15 mos	18 mos	19-23 mos	2-3 yrs	4-6 yrs	7-10 yrs	11-12 yrs	13-15 yrs	16 yrs	17-18 yrs
Hepatitis B (HepB)	1st dose	2nd dose			◄---------- 3rd dose ----------►												
Rotavirus (RV) RV1 (2-dose series); RV5 (3-dose series)			1st dose	2nd dose	See Notes												
Diphtheria, tetanus, & acellular pertussis (DTaP: <7 yrs)			1st dose	2nd dose	3rd dose			◄----- 4th dose ------►				5th dose					
Haemophilus influenzae type b (Hib)			1st dose	2nd dose	See Notes		◄-- 3rd or 4th dose, See Notes --►										
Pneumococcal conjugate (PCV13)			1st dose	2nd dose	3rd dose		◄----- 4th dose -----►										
Inactivated poliovirus (IPV: <18 yrs)			1st dose	2nd dose	◄---------- 3rd dose ----------►							4th dose					
Influenza (IIV)					Annual vaccination 1 or 2 doses								Annual vaccination 1 dose only				
or													or				
Influenza (LAIV)											Annual vaccination 1 or 2 doses		Annual vaccination 1 dose only				
Measles, mumps, rubella (MMR)					See Notes		◄----- 1st dose -----►					2nd dose					
Varicella (VAR)							◄----- 1st dose -----►					2nd dose					
Hepatitis A (HepA)					See Notes		2-dose series, See Notes										
Meningococcal (MenACWY-D ≥9 mos; MenACWY-CRM ≥2 mos)			See Notes											1st dose		2nd dose	
Tetanus, diphtheria, & acellular pertussis (Tdap: ≥7 yrs)														Tdap			
Human papillomavirus (HPV)														See Notes			
Meningococcal B															See Notes		
Pneumococcal polysaccharide (PPSV23)											See Notes						

Range of recommended ages for all children

Range of recommended ages for catch-up immunization

Range of recommended ages for certain high-risk groups

Range of recommended ages for non-high-risk groups that may receive vaccine, subject to individual clinical decision-making

No recommendation

FIG. 316.1 (A) Recommended child and adolescent immunization schedule for ages 18 years or younger, United States, 2019. (B) Catch-up immunization schedule for persons aged 4 months to 18 years who start late or who are more than 1 month behind—United States, 2019. (C) Footnotes for both schedules. (D) Child and adolescent schedule by medical and other indications, United States, 2019. *(From Centers for Disease Control and Prevention. Recommended child and adolescent immunization schedule for ages 18 years or younger, United States, 2019.* www.cdc.gov/vaccines/schedules/hcp/child-adolescent.html. *Accessed February 8, 2019.)*

Table 2 Catch-up immunization schedule for persons aged 4 months—18 years who start late or who are more than 1 month behind, United States, 2019

The figure below provides catch-up schedules and minimum intervals between doses for children whose vaccinations have been delayed. A vaccine series does not need to be restarted, regardless of the time that has elapsed between doses. Use the section appropriate for the child's age. Always use this table in conjunction with Table 1 and the notes that follow.

Children age 4 months through 6 years					
Vaccine	**Minimum Age for Dose 1**	**Minimum Interval Between Doses**			
		Dose 1 to Dose 2	**Dose 2 to Dose 3**	**Dose 3 to Dose 4**	**Dose 4 to Dose 5**
Hepatitis B	Birth	**4 weeks**	**8 weeks *and* at least 16 weeks after first dose.** Minimum age for the final dose is 24 weeks.		
Rotavirus	6 weeks Maximum age for first dose is 14 weeks, 6 days	**4 weeks**	**4 weeks** Maximum age for final dose is 8 months, 0 days.		
Diphtheria, tetanus, and acellular pertussis	6 weeks	**4 weeks**	**4 weeks**	**6 months**	**6 months**
Haemophilus influenzae type b	6 weeks	**No further doses needed** if first dose was administered at age 15 months or older. **4 weeks** if first dose was administered before the 1st birthday. **8 weeks (as final dose)** if first dose was administered at age 12 through 14 months.	**No further doses needed** if previous dose was administered at age 15 months or older. **4 weeks** if current age is younger than 12 months ***and*** first dose was administered at younger than age 7 months, ***and*** at least 1 previous dose was PRP-T (ActHib, Pentacel, Hiberix) or unknown. **8 weeks *and* age 12 through 59 months (as final dose)** if current age is younger than 12 months ***and*** first dose was administered at age 7 through 11 months; OR if current age is 12 through 59 months ***and*** first dose was administered before the 1st birthday, ***and*** second dose administered at younger than 15 months; OR if both doses were PRP-OMP (PedvaxHIB; Comvax) ***and*** were administered before the 1st birthday.	**8 weeks (as final dose)** This dose only necessary for children age 12 through 59 months who received 3 doses before the 1st birthday.	
Pneumococcal conjugate	6 weeks	**No further doses needed** for healthy children if first dose was administered at age 24 months or older. **4 weeks** if first dose administered before the 1st birthday. **8 weeks (as final dose for healthy children)** if first dose was administered at the 1st birthday or after.	**No further doses needed** for healthy children if previous dose administered at age 24 months or older. **4 weeks** if current age is younger than 12 months and previous dose given at <7 months old. **8 weeks (as final dose for healthy children)** if previous dose given between 7-11 months (wait until at least 12 months old); OR if current age is 12 months or older and at least 1 dose was given before age 12 months.	**8 weeks (as final dose)** This **dose** only necessary for children age 12 through 59 months who received 3 doses before age 12 months or for children at high risk who received 3 doses at any age.	
Inactivated poliovirus	6 weeks	**4 weeks**	4 weeks if current age is < 4 years. 6 months (as final dose) if current age is 4 years or older.	**6 months** (minimum age 4 years for final dose).	
Measles, mumps, rubella	12 months	**4 weeks**			
Varicella	12 months	**3 months**			
Hepatitis A	12 months	**6 months**			
Meningococcal	2 months MenACWY-CRM 9 months MenACWY-D	**8 weeks**	See Notes	See Notes	
Children and adolescents age 7 through 18 years					
Meningococcal	Not Applicable (N/A)	**8 weeks**			
Tetanus, diphtheria; tetanus, diphtheria, and acellular pertussis	7 years	**4 weeks**	**4 weeks** if first dose of DTaP/DT was administered before the 1st birthday. **6 months (as final dose)** if first dose of DTaP/DT or Tdap/Td was administered at or after the 1st birthday.	**6 months** if first dose of DTaP/DT was administered before the 1st birthday.	
Human papillomavirus	9 years	**Routine dosing intervals are recommended.**			
Hepatitis A	N/A	**6 months**			
Hepatitis B	N/A	**4 weeks**	**8 weeks *and*** at least 16 weeks after first dose.		
Inactivated poliovirus	N/A	**4 weeks**	**6 months** A fourth dose is not necessary if the third dose was administered at age 4 years or older and at least 6 months after the previous dose.	A fourth dose of IPV is indicated if all previous doses were administered at <4 years or if the third dose was administered <6 months after the second dose.	
Measles, mumps, rubella	N/A	**4 weeks**			
Varicella	N/A	**3 months** if younger than age 13 years. **4 weeks** if age 13 years or older.			

FIG. 316.1, cont'd

Continued

Notes Recommended Child and Adolescent Immunization Schedule for ages 18 years or younger, United States, 2019

For vaccine recommendations for persons 19 years of age and older, see the Recommended Adult Immunization Schedule.

Additional information

- Consult relevant ACIP statements for detailed recommendations at www.cdc.gov/vaccines/hcp/acip-recs/index.html.
- For information on contraindications and precautions for the use of a vaccine, consult the General Best Practice Guidelines for Immunization and relevant ACIP statements at www.cdc.gov/vaccines/hcp/acip-recs/index.html.
- For calculating intervals between doses, 4 weeks = 28 days. Intervals of ≥4 months are determined by calendar months.
- Within a number range (e.g., 12–18), a dash (–) should be read as "through."
- Vaccine doses administered ≤4 days before the minimum age or interval are considered valid. Doses of any vaccine administered ≥5 days earlier than the minimum age or minimum interval should not be counted as valid and should be repeated as age-appropriate. The repeat dose should be spaced after the invalid dose by the recommended minimum interval. For further details, see Table 3-1, Recommended and minimum ages and intervals between vaccine doses, in General Best Practice Guidelines for Immunization at www.cdc.gov/vaccines/hcp/acip-recs/general-recs/timing.html.
- Information on travel vaccine requirements and recommendations is available at wwwnc.cdc.gov/travel/.
- For vaccination of persons with immunodeficiencies, see Table 8-1, Vaccination of persons with primary and secondary immunodeficiencies, in General Best Practice Guidelines for Immunization at www.cdc.gov/vaccines/hcp/acip-recs/general-recs/immunocompetence.html, and Immunization in Special Clinical Circumstances (In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:67–111).
- For information regarding vaccination in the setting of a vaccine-preventable disease outbreak, contact your state or local health department.
- The National Vaccine Injury Compensation Program (VICP) is a no-fault alternative to the traditional legal system for resolving vaccine injury claims. All routine child and adolescent vaccines are covered by VICP except for pneumococcal polysaccharide vaccine (PPSV23). For more information, see www.hrsa.gov/vaccinecompensation/index.html.

Diphtheria, tetanus, and pertussis (DTaP) vaccination (minimum age: 6 weeks [4 years for Kinrix or Quadracel])

Routine vaccination

- 5-dose series at 2, 4, 6, 15–18 months, 4–6 years
  - **Prospectively:** Dose 4 may be given as early as age 12 months if at least 6 months have elapsed since dose 3.
  - **Retrospectively:** A 4th dose that was inadvertently given as early as 12 months may be counted if at least 4 months have elapsed since dose 3.

Catch-up vaccination

- Dose 5 is not necessary if dose 4 was administered at age 4 years or older.
- For other catch-up guidance, see Table 2.

Haemophilus influenzae type b vaccination (minimum age: 6 weeks)

Routine vaccination

- **ActHIB, Hiberix, or Pentacel:** 4-dose series at 2, 4, 6, 12–15 months
- **PedvaxHIB:** 3-dose series at 2, 4, 12–15 months

Catch-up vaccination

- **Dose 1 at 7–11 months:** Administer dose 2 at least 4 weeks later and dose 3 (final dose) at 12–15 months or 8 weeks after dose 2 (whichever is later).
- **Dose 1 at 12–14 months:** Administer dose 2 (final dose) at least 8 weeks after dose 1.
- **Dose 1 before 12 months and dose 2 before 15 months:** Administer dose 3 (final dose) 8 weeks after dose 2.
- **2 doses of PedvaxHIB before 12 months:** Administer dose 3 (final dose) at 12–59 months and at least 8 weeks after dose 2.
- **Unvaccinated at 15–59 months:** 1 dose
- For other catch-up guidance, see Table 2.

Special situations

- **Chemotherapy or radiation treatment:**
  12–59 months
  - Unvaccinated or only 1 dose before age 12 months: 2 doses, 8 weeks apart
  - 2 or more doses before age 12 months: 1 dose at least 8 weeks after previous dose

  Doses administered within 14 days of starting therapy or during therapy should be repeated at least 3 months after therapy completion.
- **Hematopoietic stem cell transplant (HSCT):**
  - 3-dose series 4 weeks apart starting 6 to 12 months after successful transplant regardless of Hib vaccination history
- **Anatomic or functional asplenia (including sickle cell disease):**
  12–59 months
  - Unvaccinated or only 1 dose before 12 months: 2 doses, 8 weeks apart
  - 2 or more doses before 12 months:1 dose at least 8 weeks after previous dose

  Unvaccinated persons age 5 years or older*
  - 1 dose
- **Elective splenectomy:**
  Unvaccinated persons age 15 months or older*
  - 1 dose (preferably at least 14 days before procedure)
- **HIV infection:**
  12–59 months
  - Unvaccinated or only 1 dose before age 12 months: 2 doses, 8 weeks apart
  - 2 or more doses before age 12 months: 1 dose at least 8 weeks after previous dose

  Unvaccinated persons age 5–18 years*
  - 1 dose
- **Immunoglobulin deficiency, early component complement deficiency:**
  12–59 months
  - Unvaccinated or only 1 dose before age 12 months: 2 doses, 8 weeks apart
  - 2 or more doses before age 12 months: 1 dose at least 8 weeks after previous dose

**Unvaccinated* = Less than routine series (through 14 months) OR no doses (14 months or older)

FIG. 316.1, cont'd

Notes

Recommended Child and Adolescent Immunization Schedule for ages 18 years or younger, United States, 2019

Hepatitis A vaccination (minimum age: 12 months for routine vaccination)

Routine vaccination

- 2-dose series (**Havrix** 6–12 months apart or **Vaqta** 6–18 months apart, minimum interval 6 months); a series begun before the 2nd birthday should be completed even if the child turns 2 before the second dose is administered.

Catch-up vaccination

- Anyone 2 years of age or older may receive HepA vaccine if desired. Minimum interval between doses: 6 months
- Adolescents 18 years and older may receive the combined HepA and HepB vaccine, **Twinrix**, as a 3-dose series (0, 1, and 6 months) or 4-dose series (0, 7, and 21–30 days, followed by a dose at 12 months).

International travel

- Persons traveling to or working in countries with high or intermediate endemic hepatitis A (wwwnc.cdc.gov/travel/):
  - **Infants age 6–11 months**: 1 dose before departure; revaccinate with 2 doses, separated by 6–18 months, between 12 to 23 months of age.
  - **Unvaccinated age 12 months and older**: 1st dose as soon as travel considered

Special situations

At risk for hepatitis A infection: 2-dose series as above

- **Chronic liver disease**
- **Clotting factor disorders**
- **Men who have sex with men**
- **Injection or non-injection drug use**
- **Homelessness**
- **Work with hepatitis A virus** in research laboratory or nonhuman primates with hepatitis A infection
- **Travel** in countries with high or intermediate endemic hepatitis A
- **Close, personal contact with international adoptee** (e.g., household or regular babysitting) in first 60 days after arrival from country with high or intermediate endemic hepatitis A (administer dose 1 as soon as adoption is planned, at least 2 weeks before adoptee's arrival)

Hepatitis B vaccination (minimum age: birth)

Birth dose (monovalent HepB vaccine only)

- **Mother is HBsAg-negative:** 1 dose within 24 hours of birth for **all** medically stable infants ≥2,000 grams. Infants <2,000 grams: administer 1 dose at chronological age 1 month or hospital discharge.
- **Mother is HBsAg-positive:**
  - Administer **HepB vaccine** and **0.5 mL of hepatitis B immune globulin (HBIG)** (at separate anatomic sites) within 12 hours of birth, regardless of birth weight. For infants <2,000 grams, administer 3 additional doses of vaccine (total of 4 doses) beginning at age 1 month.
  - Test for HBsAg and anti-HBs at age 9–12 months. If HepB series is delayed, test 1–2 months after final dose.
- **Mother's HBsAg status is unknown:**
  - Administer **HepB vaccine** within 12 hours of birth, regardless of birth weight.
  - For infants <2,000 grams, administer **0.5 mL of HBIG** in addition to HepB vaccine within 12 hours of birth. Administer 3 additional doses of vaccine (total of 4 doses) beginning at age 1 month.
  - Determine mother's HBsAg status as soon as possible. If mother is HBsAg-positive, administer **0.5 mL of HBIG** to infants ≥2,000 grams as soon as possible, but no later than 7 days of age.

Routine series

- 3-dose series at 0, 1–2, 6–18 months (use monovalent HepB vaccine for doses administered before age 6 weeks)
- Infants who did not receive a birth dose should begin the series as soon as feasible (see Table 2).
- Administration of **4 doses** is permitted when a combination vaccine containing HepB is used after the birth dose.
- **Minimum age** for the final (3rd or 4th) dose: 24 weeks
- **Minimum intervals:** dose 1 to dose 2: 4 weeks / dose 2 to dose 3: 8 weeks / dose 1 to dose 3: 16 weeks (when 4 doses are administered, substitute "dose 4" for "dose 3" in these calculations)

Catch-up vaccination

- Unvaccinated persons should complete a 3-dose series at 0, 1–2, 6 months.
- Adolescents age 11–15 years may use an alternative 2-dose schedule with at least 4 months between doses (adult formulation **Recombivax HB** only).
- Adolescents 18 years and older may receive a 2-dose series of HepB **(Heplisav-B)** at least 4 weeks apart.
- Adolescents 18 years and older may receive the combined HepA and HepB vaccine, **Twinrix**, as a 3-dose series (0, 1, and 6 months) or 4-dose series (0, 7, and 21–30 days, followed by a dose at 12 months).
- For other catch-up guidance, see Table 2.

Human papillomavirus vaccination (minimum age: 9 years)

Routine and catch-up vaccination

- HPV vaccination routinely recommended for all adolescents **age 11–12 years (can start at age 9 years)** and through age 18 years if not previously adequately vaccinated
- 2- or 3-dose series depending on age at initial vaccination:
  - **Age 9 through 14 years at initial vaccination**: 2-dose series at 0, 6–12 months (minimum interval: 5 months; repeat dose if administered too soon)
  - **Age 15 years or older at initial vaccination**: 3-dose series at 0, 1–2 months, 6 months (minimum intervals: dose 1 to dose 2: 4 weeks / dose 2 to dose 3: 12 weeks / dose 1 to dose 3: 5 months; repeat dose if administered too soon)
- If completed valid vaccination series with any HPV vaccine, no additional doses needed

Special situations

- **Immunocompromising conditions, including HIV infection:** 3-dose series as above
- **History of sexual abuse or assault:** Start at age 9 years
- **Pregnancy:** HPV vaccination not recommended until after pregnancy; no intervention needed if vaccinated while pregnant; pregnancy testing not needed before vaccination

Inactivated poliovirus vaccination (minimum age: 6 weeks)

Routine vaccination

- 4-dose series at ages 2, 4, 6–18 months, 4–6 years; administer the final dose on or after the 4th birthday and at least 6 months after the previous dose.
- 4 or more doses of IPV can be administered before the 4th birthday when a combination vaccine containing IPV is used. However, a dose is still recommended after the 4th birthday and at least 6 months after the previous dose.

Catch-up vaccination

- In the first 6 months of life, use minimum ages and intervals only for travel to a polio-endemic region or during an outbreak.
- IPV is not routinely recommended for U.S. residents 18 years and older.

Series containing oral polio vaccine (OPV), either mixed OPV-IPV or OPV-only series:

- Total number of doses needed to complete the series is the same as that recommended for the U.S. IPV schedule. See www.cdc.gov/mmwr/volumes/66/wr/mm6601a6.htm?s_cid=mm6601a6_w.

FIG. 316.1, cont'd

Continued

Notes Recommended Child and Adolescent Immunization Schedule for ages 18 years or younger, United States, 2019

- Only trivalent OPV (tOPV) counts toward the U.S. vaccination requirements. For guidance to assess doses documented as "OPV," see www.cdc.gov/mmwr/volumes/66/wr/mm6606a7.htm?s_cid=mm6606a7_w.
- For other catch-up guidance, see Table 2.

Influenza vaccination (minimum age: 6 months [IIV], 2 years [LAIV], 18 years [RIV])

Routine vaccination

- 1 dose any influenza vaccine appropriate for age and health status annually (2 doses separated by at least 4 weeks for **children 6 months–8 years** who did not receive at least 2 doses of influenza vaccine before July 1, 2018)

Special situations

- **Egg allergy, hives only**: Any influenza vaccine appropriate for age and health status annually
- **Egg allergy more severe than hives** (e.g., angioedema, respiratory distress): Any influenza vaccine appropriate for age and health status annually in medical setting under supervision of health care provider who can recognize and manage severe allergic conditions
- **LAIV should not be used for** those with a history of severe allergic reaction to any component of the vaccine (excluding egg) or to a previous dose of any influenza vaccine, children and adolescents receiving concomitant aspirin or salicylate-containing medications, children age 2 through 4 years with a history of asthma or wheezing, those who are immunocompromised due to any cause (including immunosuppression caused by medications and HIV infection), anatomic and functional asplenia, cochlear implants, cerebrospinal fluid-oropharyngeal communication, close contacts and caregivers of severely immunosuppressed persons who require a protected environment, pregnancy, and persons who have received influenza antiviral medications within the previous 48 hours.

Measles, mumps, and rubella vaccination (minimum age: 12 months for routine vaccination)

Routine vaccination

- 2-dose series at 12–15 months, 4–6 years
- Dose 2 may be administered as early as 4 weeks after dose 1.

Catch-up vaccination

- Unvaccinated children and adolescents: 2 doses at least 4 weeks apart
- The maximum age for use of *MMRV* is 12 years.

Special situations

International travel

- **Infants age 6–11 months:** 1 dose before departure; revaccinate with 2 doses at 12–15 months (12 months for children in high-risk areas) and dose 2 as early as 4 weeks later.
- **Unvaccinated children age 12 months and older:** 2-dose series at least 4 weeks apart before departure

Meningococcal serogroup A,C,W,Y vaccination (minimum age: 2 months [MenACWY-CRM, Menveo], 9 months [MenACWY-D, Menactra])

Routine vaccination

- 2-dose series: 11–12 years, 16 years

Catch-up vaccination

- Age 13–15 years: 1 dose now and booster at age 16–18 years (minimum interval: 8 weeks)
- Age 16–18 years: 1 dose

Special situations

Anatomic or functional asplenia (including sickle cell disease), HIV infection, persistent complement component deficiency, eculizumab use:

- **Menveo**
  - Dose 1 at age 8 weeks: 4-dose series at 2, 4, 6, 12 months
  - Dose 1 at age 7–23 months: 2-dose series (dose 2 at least 12 weeks after dose 1 and after the 1st birthday)
  - Dose 1 at age 24 months or older: 2-dose series at least 8 weeks apart
- **Menactra**
  - **Persistent complement component deficiency:**
    - Age 9–23 months: 2 doses at least 12 weeks apart
    - Age 24 months or older: 2 doses at least 8 weeks apart
  - **Anatomic or functional asplenia, sickle cell disease, or HIV infection:**
    - **Age 9–23 months**: Not recommended
    - **24 months or older**: 2 doses at least 8 weeks apart
    - **Menactra** must be administered at least 4 weeks after completion of PCV13 series.

Travel in countries with hyperendemic or epidemic meningococcal disease, including countries in the African meningitis belt or during the Hajj (wwwnc.cdc.gov/travel/)**:**

- Children age less than 24 months:
  - **Menveo (age 2–23 months):**
    - Dose 1 at 8 weeks: 4-dose series at 2, 4, 6, 12 months
    - Dose 1 at 7–23 months: 2-dose series (dose 2 at least 12 weeks after dose 1 and after the 1st birthday)
  - **Menactra (age 9–23 months):**
    - 2-dose series (dose 2 at least 12 weeks after dose 1; dose 2 may be administered as early as 8 weeks after dose 1 in travelers)
- Children age 2 years or older: 1 dose **Menveo** or **Menactra**

First-year college students who live in residential housing (if not previously vaccinated at age 16 years or older) or military recruits:

- 1 dose **Menveo** or **Menactra**

Note: Menactra should be administered either before or at the same time as DTaP. For MenACWY booster dose recommendations for groups listed under "Special situations" above and additional meningococcal vaccination information, see meningococcal *MMWR* publications at www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/mening.html.

Meningococcal serogroup B vaccination (minimum age: 10 years [MenB-4C, Bexsero; MenB-FHbp, Trumenba])

Clinical discretion

- MenB vaccine may be administered based on individual clinical decision to **adolescents not at increased risk** age 16–23 years (preferred age 16–18 years):
- **Bexsero:** 2-dose series at least 1 month apart
- **Trumenba:** 2-dose series at least 6 months apart; if dose 2 is administered earlier than 6 months, administer a 3rd dose at least 4 months after dose 2.

Special situations

Anatomic or functional asplenia (including sickle cell disease), persistent complement component deficiency, eculizumab use:

- **Bexsero:** 2-dose series at least 1 month apart
- **Trumenba:** 3-dose series at 0, 1–2, 6 months

Bexsero and **Trumenba** are not interchangeable; the same product should be used for all doses in a series.
For additional meningococcal vaccination information, see meningococcal *MMWR* publications at www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/mening.html.

FIG. 316.1, cont'd

Notes

Recommended Child and Adolescent Immunization Schedule for ages 18 years or younger, United States, 2019

Pneumococcal vaccination (minimum age: 6 weeks [PCV13], 2 years [PPSV23])

Routine vaccination with PCV13

- 4-dose series at 2, 4, 6, 12–15 months

Catch-up vaccination with PCV13

- 1 dose for healthy children age 24–59 months with any incomplete* PCV13 series
- For other catch-up guidance, see Table 2.

Special situations

High-risk conditions below: When both PCV13 and PPSV23 are indicated, administer PCV13 first. PCV13 and PPSV23 should not be administered during same visit.

Chronic heart disease (particularly cyanotic congenital heart disease and cardiac failure); chronic lung disease (including asthma treated with high-dose, oral corticosteroids); diabetes mellitus:

Age 2–5 years

- Any incomplete* series with:
  - 3 PCV13 doses: 1 dose PCV13 (at least 8 weeks after any prior PCV13 dose)
  - Less than 3 PCV13 doses: 2 doses PCV13 (8 weeks after the most recent dose and administered 8 weeks apart)
- No history of PPSV23: 1 dose PPSV23 (at least 8 weeks after any prior PCV13 dose)

Age 6–18 years

- No history of PPSV23: 1 dose PPSV23 (at least 8 weeks after any prior PCV13 dose)

Cerebrospinal fluid leak, cochlear implant:

Age 2–5 years

- Any incomplete* series with:
  - 3 PCV13 doses: 1 dose PCV13 (at least 8 weeks after any prior PCV13 dose)
  - Less than 3 PCV13 doses: 2 doses PCV13, 8 weeks after the most recent dose and administered 8 weeks apart
- No history of PPSV23: 1 dose PPSV23 (at least 8 weeks after any prior PCV13 dose)

Age 6–18 years

- No history of either PCV13 or PPSV23: 1 dose PCV13, 1 dose PPSV23 at least 8 weeks later
- Any PCV13 but no PPSV23: 1 dose PPSV23 at least 8 weeks after the most recent dose of PCV13
- PPSV23 but no PCV13: 1 dose PCV13 at least 8 weeks after the most recent dose of PPSV23

Sickle cell disease and other hemoglobinopathies; anatomic or functional asplenia; congenital or acquired immunodeficiency; HIV infection; chronic renal failure; nephrotic syndrome; malignant neoplasms, leukemias, lymphomas, Hodgkin disease, and other diseases associated with treatment with immunosuppressive drugs or radiation therapy; solid organ transplantation; multiple myeloma:

Age 2–5 years

- Any incomplete* series with:
  - 3 PCV13 doses: 1 dose PCV13 (at least 8 weeks after any prior PCV13 dose)
  - Less than 3 PCV13 doses: 2 doses PCV13 (8 weeks after the most recent dose and administered 8 weeks apart)
- No history of PPSV23: 1 dose PPSV23 (at least 8 weeks after any prior PCV13 dose) and a 2nd dose of PPSV23 5 years later

Age 6–18 years

- No history of either PCV13 or PPSV23: 1 dose PCV13, 2 doses PPSV23 (dose 1 of PPSV23 administered 8 weeks after PCV13 and dose 2 of PPSV23 administered at least 5 years after dose 1 of PPSV23)
- Any PCV13 but no PPSV23: 2 doses PPSV23 (dose 1 of PPSV23 administered 8 weeks after the most recent dose of PCV13 and dose 2 of PPSV23 administered at least 5 years after dose 1 of PPSV23)
- PPSV23 but no PCV13: 1 dose PCV13 at least 8 weeks after the most recent PPSV23 dose and a 2nd dose of PPSV23 administered 5 years after dose 1 of PPSV23 and at least 8 weeks after a dose of PCV13

Chronic liver disease, alcoholism:

Age 6–18 years

- No history of PPSV23: 1 dose PPSV23 (at least 8 weeks after any prior PCV13 dose)

*An incomplete series is defined as not having received all doses in either the recommended series or an age-appropriate catch-up series. See Tables 8, 9, and 11 in the ACIP pneumococcal vaccine recommendations (www.cdc.gov/mmwr/pdf/rr/rr5911.pdf) for complete schedule details.

Rotavirus vaccination (minimum age: 6 weeks)

Routine vaccination

- **Rotarix:** 2-dose series at 2 and 4 months.
- **RotaTeq:** 3-dose series at 2, 4, and 6 months.

If any dose in the series is either **RotaTeq** or unknown, default to 3-dose series.

Catch-up vaccination

- Do not start the series on or after age 15 weeks, 0 days.
- The maximum age for the final dose is 8 months, 0 days.
- For other catch-up guidance, see Figure 2.

Tetanus, diphtheria, and pertussis (Tdap) vaccination (minimum age: 11 years for routine vaccination, 7 years for catch-up vaccination)

Routine vaccination

- **Adolescents age 11–12 years:** 1 dose Tdap
- **Pregnancy:** 1 dose Tdap during each pregnancy, preferably in early part of gestational weeks 27–36
- Tdap may be administered regardless of the interval since the last tetanus- and diphtheria-toxoid-containing vaccine.

Catch-up vaccination

- **Adolescents age 13–18 years who have not received Tdap:** 1 dose Tdap, then Td booster every 10 years
- **Persons age 7–18 years not fully immunized with DTaP:** 1 dose Tdap as part of the catch-up series (preferably the first dose); if additional doses are needed, use Td.
- **Children age 7–10 years** who receive Tdap inadvertently or as part of the catch-up series should receive the routine Tdap dose at 11–12 years.
- **DTaP inadvertently given after the 7th birthday:**
  - **Child age 7–10 years**: DTaP may count as part of catch-up series. Routine Tdap dose at 11–12 should be administered.
  - **Adolescent age 11–18 years**: Count dose of DTaP as the adolescent Tdap booster.
- For other catch-up guidance, see Table 2.
- For information on use of Tdap or Td as tetanus prophylaxis in wound management, see www.cdc.gov/mmwr/volumes/67/rr/rr6702a1.htm.

Varicella vaccination (minimum age: 12 months)

Routine vaccination

- 2-dose series: 12–15 months, 4–6 years
- Dose 2 may be administered as early as 3 months after dose 1 (a dose administered after a 4-week interval may be counted).

Catch-up vaccination

- Ensure persons age 7–18 years without evidence of immunity (see *MMWR* at www.cdc.gov/mmwr/pdf/rr/rr5604.pdf) have 2-dose series:
  - **Ages 7–12 years**: routine interval: 3 months (minimum interval: 4 weeks)
  - **Ages 13 years and older**: routine interval: 4–8 weeks (minimum interval: 4 weeks).
  - The maximum age for use of *MMRV* is 12 years.

FIG. 316.1, cont'd

Continued

Table 3 Recommended Child and Adolescent Immunization Schedule by Medical Indication United States, 2019

VACCINE	INDICATION									
	Pregnancy	Immunocompromised status (excluding HIV infection)	HIV infection CD4+ count[1]		Kidney failure, end-stage renal disease, on hemodialysis	Heart disease, chronic lung disease	CSF leaks/ cochlear implants	Asplenia and persistent complement component deficiencies	Chronic liver disease	Diabetes
			<15% and total CD4 cell count of <200/mm3	≥15% and total CD4 cell count of ≥200/mm3						
Hepatitis B										
Rotavirus		SCID[2]								
Diphtheria, tetanus, & acellular pertussis (DTaP)										
Haemophilus influenzae type b										
Pneumococcal conjugate										
Inactivated poliovirus										
Influenza (IIV)										
or										
Influenza (LAIV)						Asthma, wheezing: 2-4yrs[3]				
Measles, mumps, rubella										
Varicella										
Hepatitis A										
Meningococcal ACWY										
Tetanus, diphtheria, & acellular pertussis (Tdap)										
Human papillomavirus										
Meningococcal B										
Pneumococcal polysaccharide										

- Vaccination according to the routine schedule recommended
- Recommended for persons with an additional risk factor for which the vaccine would be indicated
- Vaccination is recommended, and additional doses may be necessary based on medical condition. See Notes.
- Contraindicated or use not recommended—vaccine should not be administered because of risk for serious adverse reaction
- Precaution—vaccine might be indicated if benefit of protection outweighs risk of adverse reaction
- Delay vaccination until after pregnancy if vaccine indicated
- No recommendation

1 For additional information regarding HIV laboratory parameters and use of live vaccines, see the General Best Practice Guidelines for Immunization "Altered Immunocompetence" at www.cdc.gov/vaccines/hcp/acip-recs/general-recs/immunocompetence.html, and Table 4-1 (footnote D) at: www.cdc.gov/vaccines/hcp/acip-recs/general-recs/contraindications.html.
2 Severe Combined Immunodeficiency
3 LAIV contraindicated for children 2–4 years of age with asthma or wheezing during the preceding 12 months.

FIG. 316.1, cont'd

the United States, use of BCG should be considered for individuals, such as infants, whose skin test results are negative and who have prolonged, close contact with patients with active tuberculosis who are untreated, are ineffectively treated, or have antibiotic-resistant infection. BCG also may be considered for health care providers in areas in which multidrug-resistant *Mycobacterium tuberculosis* infection has become a significant problem.[88]

A single dose of vaccine is administered intradermally or by the percutaneous route. (The Tice strain licensed in the United States is approved only for percutaneous administration.) Known adverse reactions include regional adenitis, disseminated BCG infection, and osteitis caused by the BCG organism. Adenitis occurs in about 1% to 10% of vaccinees, whereas disseminated infections and osteitis are quite rare (about 1 case per 1 million vaccinees). The risk for developing osteitis after BCG vaccination varies by country; in one review, this risk ranged from 0.01 cases per million vaccinees in Japan to 32.5 and 43.4 cases per million vaccinees in Sweden and Finland, respectively.[89] Immunocompromised individuals should not receive the vaccine because of increased risk for disseminated BCG infection.[88]

Cholera Vaccine

A killed whole-cell cholera vaccine was available in the United States from the 1940s until 2001. [90] Killed whole-cell vaccines are still available in some countries, and improved killed vaccines are licensed in some countries. Two oral whole-cell inactivated vaccines, including one that is combined with the B subunit of cholera toxin, are available in some parts of the world, as is an oral live-attenuated vaccine with a critical moiety of the gene for the cholera toxin deleted.[91,91a] Killed oral cholera vaccines are increasingly being used as important components of cholera prevention in epidemic and endemic settings. A live oral vaccine (CVD 103-HgR or Vaxchora, manufactured by PaxVax) was licensed in the United States in 2016. The vaccine is administered as a single dose with a buffer salt to neutralize stomach acid. It is recommended for travelers 18 to 64 years of age to an area of active cholera transmission. Vaxchora should be administered 8 hours or more after a dose of oral typhoid vaccine.

Diphtheria Toxoid

Diphtheria toxoid is a purified preparation of inactivated diphtheria toxin. It is highly effective in inducing antibodies that will prevent disease, although antibodies may not prevent acquisition or carriage of the organism. In the United States, the toxoid is available in adsorbed form, combined with tetanus toxoid (adult formulation, Td, and pediatric formulation, DT) or with tetanus toxoid and acellular pertussis vaccine (DTaP, childhood formulation; or Tdap, adult formulation). Single-antigen diphtheria toxoid is not distributed in the United States. Two dosage formulations are available: one for use in children through 6 years of age, and one for use in older children and adults. The adult formulation has a lower concentration of diphtheria toxoid (≤2.5 limit of flocculation units [Lf]) than the childhood formulation (6.7–25 Lf) because local reactions are thought to relate to both age and dosage. With all formulations, levels of antitoxin considered protective are induced in more than 90% of recipients who complete the schedule.[54,92,93]

Immunization against diphtheria is recommended for all residents in the United States. For children younger than 7 years with no contraindications to pertussis immunization, DTaP is recommended, and the primary series is three doses administered 4 to 8 weeks apart, followed by a first booster dose 6 to 12 months later and a second booster dose at school entry (4–6 years of age). For infants with contraindications to pertussis vaccine, DT is administered in the same schedule as DTaP (see "Pertussis-Containing Vaccine" and Fig. 316.1). The primary immunizing series of DT (for children 1–6 years of age) or Td (for older children and adults) consists of at least two doses administered 4 to 8 weeks apart, followed by a third dose 6 to 12 months later. There is no need to restart a series if the schedule is interrupted; the next dose in the series should be given. Booster doses of Td should be given every 10 years. All persons 11 years and older should receive one dose of Tdap, which can serve as one of the recommended booster doses for diphtheria and tetanus. Persons 7 years or older not fully vaccinated with DTaP vaccine should receive one dose of Tdap as part of a catch-up series. If the dose is administered at 7 through 10 years of age, another dose of Tdap should be administered at 11 or 12 years of age. Tdap should be administered to pregnant women during every pregnancy, optimally early between gestational ages 27 weeks and 36 weeks.[71] Tdap administered during pregnancy provides passive immunity to the fetus and should protect newborns and young infants before they have time to make an active immune response to DTaP. Known adverse effects of diphtheria toxoid include local reactions and mild or moderate systemic reactions such as fever; anaphylaxis occurs rarely. Brachial neuritis appears to be a rare consequence of immunization and is most likely due to tetanus toxoid.[65] The only contraindications are in individuals who previously have had severe hypersensitivity reactions after diphtheria or tetanus toxoids or, if combined with pertussis, have had previous similar adverse events to those antigens.

Haemophilus influenzae Type b Vaccine (Hib)

Conjugated vaccines to prevent Hib invasive disease were first licensed at the end of 1987 and have replaced the earlier polysaccharide vaccines because they elicit substantially higher antibody titers and are effective in young infants.[94] The polysaccharide in these vaccines is covalently linked to protein carriers, converting them from T-lymphocyte–independent antigens to T-lymphocyte–dependent antigens. There are four available conjugate vaccines licensed for use in infants.[95] Three are single-component vaccines for prevention of Hib disease. Carrier proteins include a *Neisseria meningitidis* outer membrane protein complex (PRP-OMP) for PedVaxHib and tetanus toxoid (PRP-T) for ActHIB and Hiberix. PRP-OMP has been demonstrated to be 95% effective in a clinical trial in infants. PRP-T has been licensed for use in infants because it elicits comparable antibody responses to other conjugate vaccines that have been shown to be highly effective. A combination vaccine, DTaP-IPV/Hib, is licensed for any of the recommended first four doses during the first 2 years of life (www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm174757.htm and www.fda.gov/biologicsbloodvaccines/vaccines/approvedproducts/ucm172502.htm).[96]

The Hib component of DTaP-IPV contains PRP-T as the conjugate. PRP-OMP behaves differently from PRP-T, inducing high levels of antibody after a single dose. A second dose 2 months later increases those levels; less benefit appears to be derived from a third dose.[94] The basic series for PRP-OMP is two doses given 2 months apart beginning at 2 months of age, followed by a booster dose at 12 to 15 months of age.[94] PRP-OMP is preferred in American Indian/Alaska Native populations because of the younger peak in disease incidence. In contrast, PRP-T does not induce substantial antibody levels until the second dose, and high levels of protection are achieved only after three doses 2 months apart. The basic series for PRP-T starts at 2 months of age with three doses 2 months apart, followed by a booster dose at 12 to 15 months of age.[94] Although use of a single conjugate vaccine for the primary series is recommended, several studies have suggested that mixed sequences of Hib conjugate vaccines induce an adequate immune response.[97–99] Thus, for infants younger than 6 months, three doses of any licensed Hib vaccine administered at 2-month intervals should confer protection; a booster dose is given at 12 to 15 months of age.

For healthy infants starting immunization at 7to 11 months, two doses of any of the Hib vaccines licensed for infants should be given with at least 4 weeks between the two doses, followed by a booster dose at 12 to 15 months, provided that at least 2 months have elapsed since the second dose. Any of the conjugates can be used for the booster dose.[94]

Healthy children beginning immunization at 12 to 14 months of age can receive two doses of any conjugate, with the second dose given at least 2 months after the first dose. Healthy children who initially are immunized at 15 months or older need only one dose of any of the conjugate vaccines. Unimmunized children aged 60 months or older do not need catch-up vaccination.

High-risk conditions include functional or anatomic asplenia and immunosuppression, particularly IgG2 subclass deficiency, early complement component deficiency, HIV infection, receipt of chemotherapy or radiation therapy for malignant neoplasms, and receipt of a hematopoietic stem cell transplant (HSCT). Children who will be undergoing splenectomy and are age 15 months or older who are unvaccinated or incompletely vaccinated (which means they have received fewer doses

Text continued on p. 3791

Table 1 Recommended Adult Immunization Schedule by Age Group United States, 2019

Vaccine	19–21 years	22–26 years	27–49 years	50–64 years	≥65 years
Influenza inactivated (IIV) or **Influenza recombinant** (RIV)	1 dose annually				
or					
Influenza live attenuated (LAIV)	1 dose annually				
Tetanus, diphtheria, pertussis (Tdap or Td)	1 dose Tdap, then Td booster every 10 yrs				
Measles, mumps, rubella (MMR)	1 or 2 doses depending on indication (if born in 1957 or later)				
Varicella (VAR)	2 doses (if born in 1980 or later)				
Zoster recombinant (RZV) *(preferred)*				2 doses	
or					
Zoster live (ZVL)				1 dose	
Human papillomavirus (HPV) **Female**	2 or 3 doses depending on age at initial vaccination				
Human papillomavirus (HPV) **Male**	2 or 3 doses depending on age at initial vaccination				
Pneumococcal conjugate (PCV13)	1 dose				
Pneumococcal polysaccharide (PPSV23)	1 or 2 doses depending on indication				1 dose
Hepatitis A (HepA)	2 or 3 doses depending on vaccine				
Hepatitis B (HepB)	2 or 3 doses depending on vaccine				
Meningococcal A, C, W, Y (MenACWY)	1 or 2 doses depending on indication, then booster every 5 yrs if risk remains				
Meningococcal B (MenB)	2 or 3 doses depending on vaccine and indication				
***Haemophilus influenzae* type b** (Hib)	1 or 3 doses depending on indication				

Recommended vaccination for adults who meet age requirement, lack documentation of vaccination, or lack evidence of past infection

Recommended vaccination for adults with an additional risk factor or another indication

No recommendation

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FIG. 316.2 Recommended 2019 adult immunization schedule, by age group. See Fig. 316.4 for footnotes. *(From Centers for Disease Control and Prevention. Recommended adult immunization schedule for ages 19 years or older, United States, 2019. www.cdc.gov/vaccines/schedules/hcp/imz/adult.html. Accessed February 8, 2019.)*

Table 2 Recommended Adult Immunization Schedule by Medical Condition and Other Indications United States, 2019

Vaccine	Pregnancy	Immuno-compromised (excluding HIV infection)	HIV infection CD4 count <200	HIV infection CD4 count ≥200	Asplenia, complement deficiencies	End-stage renal disease, on hemodialysis	Heart or lung disease, alcoholism[1]	Chronic liver disease	Diabetes	Health care personnel[2]	Men who have sex with men
IIV or RIV	1 dose annually										
or										or	
LAIV	CONTRAINDICATED						PRECAUTION			1 dose annually	
Tdap or Td	1 dose Tdap each pregnancy	1 dose Tdap, then Td booster every 10 yrs									
MMR	CONTRAINDICATED			1 or 2 doses depending on indication							
VAR	CONTRAINDICATED			2 doses							
RZV *(preferred)*	DELAY					2 doses at age ≥50 yrs					
or						or					
ZVL	CONTRAINDICATED					1 dose at age ≥60 yrs					
HPV Female	DELAY	3 doses through age 26 yrs			2 or 3 doses through age 26 yrs						
HPV Male		3 doses through age 26 yrs			2 or 3 doses through age 21 yrs						2 or 3 doses through age 26 yrs
PCV13		1 dose									
PPSV23		1, 2, or 3 doses depending on age and indication									
HepA	2 or 3 doses depending on vaccine										
HepB	2 or 3 doses depending on vaccine										
MenACWY	1 or 2 doses depending on indication, then booster every 5 yrs if risk remains										
MenB	PRECAUTION	2 or 3 doses depending on vaccine and indication									
Hib		3 doses HSCT[3] recipients only			1 dose						

Recommended vaccination for adults who meet age requirement, lack documentation of vaccination, or lack evidence of past infection

Recommended vaccination for adults with an additional risk factor or another indication

Precaution—vaccine might be indicated if benefit of protection outweighs risk of adverse reaction

Delay vaccination until after pregnancy if vaccine is indicated

Contraindicated—vaccine should not be administered because of risk for serious adverse reaction

No recommendation

1. Precaution for LAIV does not apply to alcoholism. **2.** See notes for influenza; hepatitis B; measles, mumps, and rubella; and varicella vaccinations. **3.** Hematopoietic stem cell transplant.

FIG. 316.3 Recommended 2019 vaccination indicated for adults based on medical and other indications. See Fig. 316.4 for footnotes. *(From Centers for Disease Control and Prevention. Vaccines that might be indicated for adults aged 19 years or older based on medical and other indications. www.cdc.gov/vaccines/schedules/hcp/imz/adult-conditions.html. Accessed February 8, 2019.)*

Notes Recommended Adult Immunization Schedule United States, 2019

Haemophilus influenzae type b vaccination

Special situations

- **Anatomical or functional asplenia (including sickle cell disease)**: 1 dose Hib if previously did not receive Hib; if elective splenectomy, 1 dose Hib, preferably at least 14 days before splenectomy
- **Hematopoietic stem cell transplant** (HSCT): 3-dose series Hib 4 weeks apart starting 6–12 months after successful transplant, regardless of Hib vaccination history

Hepatitis A vaccination

Routine vaccination

- **Not at risk but want protection from hepatitis A** (identification of risk factor not required): 2-dose series HepA (Havrix 6–12 months apart or Vaqta 6–18 months apart [minimum interval: 6 months]) or 3-dose series HepA-HepB (Twinrix at 0, 1, 6 months [minimum intervals: 4 weeks between doses 1 and 2, 5 months between doses 2 and 3])

Special situations

- **At risk for hepatitis A virus infection**: 2-dose series HepA or 3-dose series HepA-HepB as above
  - **Chronic liver disease**
  - **Clotting factor disorders**
  - **Men who have sex with men**
  - **Injection or non-injection drug use**
  - **Homelessness**
  - **Work with hepatitis A virus** in research laboratory or nonhuman primates with hepatitis A virus infection
  - **Travel in countries with high or intermediate endemic hepatitis A**
  - **Close personal contact with international adoptee** (e.g., household, regular babysitting) in first 60 days after arrival from country with high or intermediate endemic hepatitis A (administer dose 1 as soon as adoption is planned, at least 2 weeks before adoptee's arrival)

Hepatitis B vaccination

Routine vaccination

- **Not at risk but want protection from hepatitis B** (identification of risk factor not required): 2- or 3-dose series HepB (2-dose series Heplisav-B at least 4 weeks apart [2-dose series HepB only applies when 2 doses of Heplisav-B are used at least 4 weeks apart] or 3-dose series Engerix-B or Recombivax HB at 0, 1, 6 months [minimum intervals: 4 weeks between doses 1 and 2, 8 weeks between doses 2 and 3, 16 weeks between doses 1 and 3]) or 3-dose series HepA-HepB (Twinrix at 0, 1, 6 months [minimum intervals: 4 weeks between doses 1 and 2, 5 months between doses 2 and 3])

Special situations

- **At risk for hepatitis B virus infection**: 2-dose (Heplisav-B) or 3-dose (Engerix-B, Recombivax HB) series HepB, or 3-dose series HepA-HepB as above
  - **Hepatitis C virus infection**
  - **Chronic liver disease** (e.g., cirrhosis, fatty liver disease, alcoholic liver disease, autoimmune hepatitis, alanine aminotransferase [ALT] or aspartate aminotransferase [AST] level greater than twice upper limit of normal)
  - **HIV infection**
  - **Sexual exposure risk** (e.g., sex partners of hepatitis B surface antigen (HBsAg)-positive persons; sexually active persons not in mutually monogamous relationships, persons seeking evaluation or treatment for a sexually transmitted infection, men who have sex with men)
  - **Current or recent injection drug use**
  - **Percutaneous or mucosal risk for exposure to blood** (e.g., household contacts of HBsAg-positive persons; residents and staff of facilities for developmentally disabled persons; health care and public safety personnel with reasonably anticipated risk for exposure to blood or blood-contaminated body fluids; hemodialysis, peritoneal dialysis, home dialysis, and predialysis patients; persons with diabetes mellitus age younger than 60 years and, at discretion of treating clinician, those age 60 years or older)
  - **Incarcerated persons**
  - **Travel in countries with high or intermediate endemic hepatitis B**

Human papillomavirus vaccination

Routine vaccination

- **Females through age 26 years and males through age 21 years:** 2- or 3-dose series HPV vaccine depending on age at initial vaccination; males age 22 through 26 years may be vaccinated based on individual clinical decision (HPV vaccination routinely recommended at age 11–12 years)
- **Age 15 years or older at initial vaccination**: 3-dose series HPV vaccine at 0, 1–2, 6 months (minimum intervals: 4 weeks between doses 1 and 2, 12 weeks between doses 2 and 3, 5 months between doses 1 and 3; repeat dose if administered too soon)
- **Age 9 through 14 years at initial vaccination and received 1 dose, or 2 doses less than 5 months apart**: 1 dose HPV vaccine
- **Age 9 through 14 years at initial vaccination and received 2 doses at least 5 months apart**: HPV vaccination complete, no additional dose needed
- If completed valid vaccination series with any HPV vaccine, no additional doses needed

Special situations

- **Immunocompromising conditions (including HIV infection) through age 26 years**: 3-dose series HPV vaccine at 0, 1–2, 6 months as above
- **Men who have sex with men and transgender persons through age 26 years**: 2- or 3-dose series HPV vaccine depending on age at initial vaccination as above
- **Pregnancy through age 26 years**: HPV vaccination not recommended until after pregnancy; no intervention needed if vaccinated while pregnant; pregnancy testing not needed before vaccination

FIG. 316.4 Footnotes: recommended immunization schedule for adults aged 19 years and older—United States, 2019. *(From Centers for Disease Control and Prevention. Recommended adult immunization schedule, by vaccine and age group.* www.cdc.gov/vaccines/schedules/downloads/adult/adult-combined-schedule.pdf*. Accessed February 8, 2019.)*

Notes Recommended Adult Immunization Schedule United States, 2019

Influenza vaccination

Routine vaccination

- **Persons age 6 months or older**: 1 dose IIV, RIV, or LAIV appropriate for age and health status annually
- For additional guidance, see www.cdc.gov/flu/professionals/index.htm

Special situations

- **Egg allergy, hives only**: 1 dose IIV, RIV, or LAIV appropriate for age and health status annually
- **Egg allergy more severe than hives** (e.g., angioedema, respiratory distress): 1 dose IIV, RIV, or LAIV appropriate for age and health status annually in medical setting under supervision of health care provider who can recognize and manage severe allergic conditions
- **Immunocompromising conditions (including HIV infection), anatomical or functional asplenia, pregnant women, close contacts and caregivers of severely immunocompromised persons in protected environment, use of influenza antiviral medications in previous 48 hours, with cerebrospinal fluid leak or cochlear implant**: 1 dose IIV or RIV annually (LAIV not recommended)
- **History of Guillain-Barré syndrome within 6 weeks of previous dose of influenza vaccine**: Generally should not be vaccinated

Measles, mumps, and rubella vaccination

Routine vaccination

- **No evidence of immunity to measles, mumps, or rubella**: 1 dose MMR
  - Evidence of immunity: Born before 1957 (except health care personnel [see below]), documentation of receipt of MMR, laboratory evidence of immunity or disease (diagnosis of disease without laboratory confirmation is not evidence of immunity)

Special situations

- **Pregnancy with no evidence of immunity to rubella**: MMR contraindicated during pregnancy; after pregnancy (before discharge from health care facility), 1 dose MMR
- **Non-pregnant women of childbearing age with no evidence of immunity to rubella**: 1 dose MMR
- **HIV infection with CD4 count ≥200 cells/μL for at least 6 months and no evidence of immunity to measles, mumps, or rubella**: 2-dose series MMR at least 4 weeks apart; MMR contraindicated in HIV infection with CD4 count <200 cells/μL
- **Severe immunocompromising conditions**: MMR contraindicated
- **Students in postsecondary educational institutions, international travelers, and household or close personal contacts of immunocompromised persons with no evidence of immunity to measles, mumps, or rubella**: 1 dose MMR if previously received 1 dose MMR, or 2-dose series MMR at least 4 weeks apart if previously did not receive any MMR
- **Health care personnel born in 1957 or later with no evidence of immunity to measles, mumps, or rubella**: 2-dose series MMR at least 4 weeks apart for measles or mumps, or at least 1 dose MMR for rubella; if born before 1957, consider 2-dose series MMR at least 4 weeks apart for measles or mumps, or 1 dose MMR for rubella

Meningococcal vaccination

Special situations for MenACWY

- **Anatomical or functional asplenia (including sickle cell disease), HIV infection, persistent complement component deficiency, eculizumab use**: 2-dose series MenACWY (Menactra, Menveo) at least 8 weeks apart and revaccinate every 5 years if risk remains
- **Travel in countries with hyperendemic or epidemic meningococcal disease, microbiologists routinely exposed to *Neisseria meningitidis***: 1 dose MenACWY and revaccinate every 5 years if risk remains
- **First-year college students who live in residential housing (if not previously vaccinated at age 16 years or older) and military recruits**: 1 dose MenACWY

Special situations for MenB

- **Anatomical or functional asplenia (including sickle cell disease), persistent complement component deficiency, eculizumab use, microbiologists routinely exposed to *Neisseria meningitidis***: 2-dose series MenB-4C (Bexsero) at least 1 month apart, or 3-dose series MenB-FHbp (Trumenba) at 0, 1–2, 6 months (if dose 2 was administered at least 6 months after dose 1, dose 3 not needed); MenB-4C and MenB-FHbp are not interchangeable (use same product for all doses in series)
- **Pregnancy**: Delay MenB until after pregnancy unless at increased risk and vaccination benefit outweighs potential risks
- **Healthy adolescents and young adults age 16 through 23 years (age 16 through 18 years preferred) not at increased risk for meningococcal disease**: Based on individual clinical decision, may receive 2-dose series MenB-4C at least 1 month apart, or 2-dose series MenB-FHbp at 0, 6 months (if dose 2 was administered less than 6 months after dose 1, administer dose 3 at least 4 months after dose 2); MenB-4C and MenB-FHbp are not interchangeable (use same product for all doses in series)

FIG. 316.4, cont'd

Continued

Notes Recommended Adult Immunization Schedule United States, 2019

Pneumococcal vaccination

Routine vaccination

- **Age 65 years or older** (immunocompetent): 1 dose PCV13 if previously did not receive PCV13, followed by 1 dose PPSV23 at least 1 year after PCV13 and at least 5 years after last dose PPSV23
  - Previously received PPSV23 but not PCV13 at age 65 years or older: 1 dose PCV13 at least 1 year after PPSV23
  - When both PCV13 and PPSV23 are indicated, administer PCV13 first (PCV13 and PPSV23 should not be administered during same visit)

Special situations

- **Age 19 through 64 years with chronic medical conditions (chronic heart [excluding hypertension], lung, or liver disease; diabetes), alcoholism, or cigarette smoking**: 1 dose PPSV23
- **Age 19 years or older with immunocompromising conditions (congenital or acquired immunodeficiency [including B- and T-lymphocyte deficiency, complement deficiencies, phagocytic disorders, HIV infection], chronic renal failure, nephrotic syndrome, leukemia, lymphoma, Hodgkin disease, generalized malignancy, iatrogenic immunosuppression [e.g., drug or radiation therapy], solid organ transplant, multiple myeloma) or anatomical or functional asplenia (including sickle cell disease and other hemoglobinopathies)**: 1 dose PCV13 followed by 1 dose PPSV23 at least 8 weeks later, then another dose PPSV23 at least 5 years after previous PPSV23; at age 65 years or older, administer 1 dose PPSV23 at least 5 years after most recent PPSV23 (note: only 1 dose PPSV23 recommended at age 65 years or older)
- **Age 19 years or older with cerebrospinal fluid leak or cochlear implant**: 1 dose PCV13 followed by 1 dose PPSV23 at least 8 weeks later; at age 65 years or older, administer another dose PPSV23 at least 5 years after PPSV23 (note: only 1 dose PPSV23 recommended at age 65 years or older)

Tetanus, diphtheria, and pertussis vaccination

Routine vaccination

- **Previously did not receive Tdap at or after age 11 years**: 1 dose Tdap, then Td booster every 10 years

Special situations

- **Previously did not receive primary vaccination series for tetanus, diphtheria, and pertussis**: 1 dose Tdap followed by 1 dose Td at least 4 weeks after Tdap, and another dose Td 6–12 months after last Td (Tdap can be substituted for any Td dose, but preferred as first dose); Td booster every 10 years thereafter
- **Pregnancy**: 1 dose Tdap during each pregnancy, preferably in early part of gestational weeks 27–36
- For information on use of Tdap or Td as tetanus prophylaxis in wound management, see www.cdc.gov/mmwr/volumes/67/rr/rr6702a1.htm

Varicella vaccination

Routine vaccination

- **No evidence of immunity to varicella**: 2-dose series VAR 4–8 weeks apart if previously did not receive varicella-containing vaccine (VAR or MMRV [measles-mumps-rubella-varicella vaccine] for children); if previously received 1 dose varicella-containing vaccine: 1 dose VAR at least 4 weeks after first dose
  - Evidence of immunity: U.S.-born before 1980 (except for pregnant women and health care personnel [see below]), documentation of 2 doses varicella-containing vaccine at least 4 weeks apart, diagnosis or verification of history of varicella or herpes zoster by a health care provider, laboratory evidence of immunity or disease

Special situations

- **Pregnancy with no evidence of immunity to varicella**: VAR contraindicated during pregnancy; after pregnancy (before discharge from health care facility), 1 dose VAR if previously received 1 dose varicella-containing vaccine, or dose 1 of 2-dose series VAR (dose 2: 4–8 weeks later) if previously did not receive any varicella-containing vaccine, regardless of whether U.S.-born before 1980
- **Health care personnel with no evidence of immunity to varicella**: 1 dose VAR if previously received 1 dose varicella-containing vaccine, or 2-dose series VAR 4–8 weeks apart if previously did not receive any varicella-containing vaccine, regardless of whether U.S.-born before 1980
- **HIV infection with CD4 count ≥200 cells/μL with no evidence of immunity**: Consider 2-dose series VAR 3 months apart based on individual clinical decision; VAR contraindicated in HIV infection with CD4 count <200 cells/μL
- **Severe immunocompromising conditions**: VAR contraindicated

Zoster vaccination

Routine vaccination

- **Age 50 years or older**: 2-dose series RZV 2–6 months apart (minimum interval: 4 weeks; repeat dose if administered too soon) regardless of previous herpes zoster or previously received ZVL (administer RZV at least 2 months after ZVL)
- **Age 60 years or older**: 2-dose series RZV 2–6 months apart (minimum interval: 4 weeks; repeat dose if administered too soon) or 1 dose ZVL if not previously vaccinated (if previously received ZVL, administer RZV at least 2 months after ZVL); RZV preferred over ZVL

Special situations

- **Pregnancy**: ZVL contraindicated; consider delaying RZV until after pregnancy if RZV is otherwise indicated
- **Severe immunocompromising conditions (including HIV infection with CD4 count <200 cells/μL)**: ZVL contraindicated; recommended use of RZV under review

FIG. 316.4, cont'd

than the routine series through 14 months of age and no doses at 14 months or older) should receive a dose of Hib vaccine at least 2 weeks before splenectomy. If they have completed the recommended series, providers may offer an additional dose of Hib vaccine.

Children 12 through 59 months of age who are asplenic and have received fewer than two doses before 12 months of age require two doses of Hib. Persons 5 years of age or older who are asplenic and who are unvaccinated or incompletely vaccinated require one dose of Hib.

Children with HIV infection between 15 months and 18 years of age and who are unvaccinated or incompletely vaccinated require one dose of Hib. Hib vaccination is not recommended for HIV-infected adults.

Patients younger than 59 months undergoing chemotherapy or radiation therapy who receive doses of Hib vaccine within 2 weeks of their therapy should have these doses repeated at least 3 months after completion of therapy. Any recipient of an HSCT should be revaccinated with a three-dose regimen 6 to 12 months after a successful transplant, regardless of vaccination history; at least 4 weeks should separate the doses.[50]

Although vaccine is not indicated for children who had documented invasive Hib infection at 2 years or older, it is indicated for children younger than 2 years who had documented invasive Hib infection because of their potential inadequate antibody response after natural infection.

Hib-containing vaccines have a very good safety record.[94] Local reactions at the injection site and fever have been noted in less than 4% of vaccinees. The vaccines should not be administered if there is a history of anaphylaxis to the specific vaccine or to other vaccine components.

Hepatitis A Vaccine

There are two inactivated single-antigen hepatitis A vaccines available in the United States: Havrix (GlaxoSmithKline Biologicals, Research Triangle Park, NC) and Vaqta (Merck, Whitehouse Station, NJ). Efficacy of one 25-unit dose of Vaqta in children 2 to 16 years of age is 97%.[100,101]

Preventing hepatitis A at the community level requires widespread vaccination of children and adults.[102] In 1996, ACIP recommended hepatitis A vaccine for children at age 2 years in communities with high rates of disease and children through the teen years in outbreaks.[103] In 1999, the ACIP recommendations were expanded to include children beginning at 2 years or older living in states, counties, or communities with reported annual rates of hepatitis A of 20 per 100,000 or higher between 1987 and 1997, and vaccine was considered in states with rates above the national average of 10 cases per 100,000 population or higher.[104] In 2006, ACIP recommended that all children aged 12 to 23 months be vaccinated.[105] Children who are not vaccinated by age 2 years can be vaccinated at subsequent visits. Hepatitis A vaccine is also recommended for use among populations known to be at increased risk for infection, including persons traveling to hepatitis A–endemic areas, men who have sex with men (MSM), users of injection and noninjection drugs, persons who work with hepatitis A virus–infected primates or who do research with the virus, recipients of clotting factors, and persons who anticipate close personal contact with an international adoptee.[106] Persons with chronic liver disease may be at increased risk for fulminant hepatitis A and should also be vaccinated as well.[103] Homelessness has been associated with hepatitis A cases and outbreaks, and homelessness was approved as an indication for hepatitis A vaccination by ACIP in October 2018.[107,107a]

Havrix is recommended in a two-dose schedule, with doses separated by 6 to 12 months. The dose for children 1 to 18 years of age is 720 enzyme-linked immunosorbent assay (ELISA) units; for adults, it is 1440 ELISA units. Two doses of 25 units of Vaqta 6 to 18 months apart are recommended for persons 1 to 18 years of age, and two doses of 50 units 6 months apart are recommended for persons aged 19 years or older. The second dose is intended to produce lifelong immunity to hepatitis A. Hepatitis A vaccine is not licensed for use in children younger than 12 months. The vaccine is poorly immunogenic in infants born to women who are seropositive for hepatitis A.[14,108] Simultaneous administration with IG may decrease immunogenicity slightly but should not cause any decrease in protection.[109]

ACIP recommends hepatitis A vaccine for international travelers to countries with high or intermediate hepatitis A endemicity. Hepatitis A vaccine should be administered to infants aged 6 to 11 months traveling outside the United States. The travel-related dose for infants aged 6 to 11 months does *not* count toward the routine two-dose series; the two-dose series should be initiated at age 12 months according to the routine, age-appropriate vaccine schedule. Healthy travelers 12 months and older who have not received the hepatitis A vaccine should receive a single dose of vaccine as soon as travel is considered.[107,110] Infants younger than 6 months and travelers who elect not to receive vaccine or for whom vaccine is contraindicated should receive a single dose of IG (0.1 mL/kg). The dose is 0.2 mL/kg if the travel duration is 1 month or longer. Persons with chronic liver disease, older adults (aged >40 years), immunocompromised persons, and persons with other chronic medical conditions planning to depart to a risk area in <2 weeks should receive the initial dose of vaccine, and IG can also be simultaneously administered at a separate anatomic injection site.

Persons who have recently been exposed to hepatitis A virus and who have not received the hepatitis A vaccine previously should receive PEP as soon as possible within 2 weeks of exposure. Persons aged ≥12 months should receive a single dose of vaccine as soon as possible. Infants aged <12 months and persons for whom vaccine is contraindicated should receive IG instead of vaccine for PEP. Immunocompromised persons and persons with chronic liver disease should receive both IG and hepatitis A vaccine simultaneously at a different anatomic site, as soon as possible after exposure. For long-term immunity, the hepatitis A vaccine series should be completed with a second dose at least 6 months after the first dose; the second dose is not necessary for PEP.

The most frequent side effects are local reactions. The only contraindication is for persons with a severe allergic reaction after a previous dose or to a vaccine component.[105]

Hepatitis B Vaccine

Hepatitis B vaccine consists of purified HBsAg particles obtained either from plasma of chronic carriers or from yeast through recombinant DNA technology. In the United States, plasma-derived vaccines have been replaced by recombinant vaccines, although the former are still available abroad. There are three single-antigen hepatitis B vaccines available in the United States—Recombivax HB (Merck), Engerix-B (GlaxoSmithKline), and Heplisav-B (Dynavax).[12] Engerix-B is available as a combination product: with hepatitis A vaccine (Twinrix; GlaxoSmithKline), or DTaP and IPV (Pediarix; GlaxoSmithKline). Heplisav-B is a recombinant vaccine that contains an adjuvant, a synthetic oligodeoxynucleotide called CpG, which binds to a molecule on APCs called TLR9, stimulating an immune response to hepatitis B. Because recommended doses vary by age, the package insert should be consulted for the proper dose of each product. When initially licensed, use of vaccine was targeted to individuals at high risk for exposure to hepatitis B, including certain categories of health care personnel (those with risk for exposure to blood or blood products), hemodialysis patients, recipients of certain blood products, MSM, certain institutionalized individuals, parenteral drug abusers, and household or sexual contacts of chronic carriers of HBsAg. Vaccine continues to be indicated for these groups, and federal regulations now mandate that the vaccine be made available at no cost to all health care and public safety workers who anticipate exposure to human blood or body fluids during work.[111] In 2011, adults through 59 years of age with diabetes were added to this list of risk groups, and so providers should offer hepatitis B vaccine to all adults with diabetes younger than 60 years. Providers may offer vaccine to diabetics older than 59 years, particularly if they receive assisted blood glucose screening in a long-term care facility.[111] Failure of vaccination to have substantial impact on disease incidence when targeted only to high-risk groups, along with appreciation that hepatitis B affects larger groups in the general population (such as heterosexuals with multiple partners), has led to development of population-based control strategies.[59] In 2018, ACIP updated recommendations for individuals with chronic liver diseases to whom hepatitis B vaccine should be administered. These included but were not limited to hepatitis C virus infection, cirrhosis, fatty liver disease, alcoholic liver disease, autoimmune hepatitis, and alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels greater than twice the upper limit of normal (Fig. 316.4).[112]

Currently in the United States, universal hepatitis B vaccine is recommended within 24 hours of birth for medically stable infants weighing

≥2000 g. Primary vaccination generally consists of three IM doses administered on a 0-, 1-, and 6-month schedule. When using combination vaccines, a four-dose schedule, including a birth dose of single-antigen hepatitis B vaccine, is acceptable. Alternative vaccination schedules (e.g., 0, 1, and 4 months or 0, 2, and 4 months) have been demonstrated to elicit dose-specific and final rates of seroprotection similar to those obtained on a 0-, 1-, and 6-month schedule. It is anticipated that those immunized as infants will still be protected when they become adolescents and young adults, the greatest risk period of acute infection in the United States.[113] To protect infants at highest risk for development of chronic hepatitis B infection, all pregnant women should be screened routinely for HBsAg, preferably during an early prenatal visit. The vaccine should be administered within 12 hours of birth, along with hepatitis B IG, to infants born of HBsAg-positive mothers.

For adolescents and adults, the usual schedule is doses at 0, 1, and 6 months.[59] All adolescents who previously have not been vaccinated should receive three doses of vaccine. The final dose of vaccine must be administered at least 8 weeks after the second dose and should follow the first dose by at least 16 weeks; the minimum interval between the first and second doses is 4 weeks. An alternative two-dose regimen of one licensed hepatitis B vaccine (Recombivax) is available for routine vaccination of adolescents, with doses at 0 and 4 to 6 months. For adolescents who have not been vaccinated previously, a good time to begin is at 11 to 12 years of age, when other immunizations also are recommended.[114]

The vaccine should be administered intramuscularly to infants in the anterolateral thigh with a 1-inch 23-gauge needle and to children and adults in the deltoid region. For deltoid vaccination, a ⅝-inch 25-gauge needle may be used in children up to 9 years of age (if the skin is stretched tightly and subcutaneous tissues are not bunched), but generally a 1-inch 23-gauge needle should be used in older children and adults. Gluteal administration is associated with poorer antibody responses and is not recommended.[13] A series of three IM doses produces a protective antibody response (antibody to HBsAg ≥10 mIU/mL) in greater than 95% of infants and children, greater than 90% of adults younger than 40 years, and 75% to 90% of adults older than 40 years. Host factors, such as smoking and obesity, contribute to decreased immunogenicity of the primary vaccine series, but age is the major determinant of vaccine response. Vaccine immunogenicity also may be lower in immunocompromised patients. Follow-up for up to 30 years has shown the virtual absence of clinically significant infections in persons who initially achieved a protective antibody titer.[10] Most persons who lose detectable antibody appear to retain immunologic memory against significant infections. A small study of Alaskan children, vaccinated at birth, suggested that almost half of children lacked anamnestic responses after a booster dose 15 years later.[10] However, none of the children had been infected, as measured by the presence of core antibody. In a study by Middleman and colleagues published 7 years later, 90% of study participants (420 adolescents) immunized against hepatitis B as infants exhibited a seroprotective response to a challenge dose of vaccine.[115] Thus there is no indication at this time for booster doses of vaccine after immunization of immunocompetent children or adults. Additional experience will be necessary to know whether there will be any need for booster doses.

Alopeica has rarely been reported primarily in adults and has been reversible in most cases.[116] A number of case reports have linked hepatitis B vaccine to demyelinating syndromes, including multiple sclerosis.[117,118] However, data available do not support a causal relationship. The IOM's Immunization Safety Review Committee reviewed available data and concluded that the evidence did not support a relationship between hepatitis B vaccination in adults and multiple sclerosis; the evidence was inadequate to accept or reject a causal relationship with other demyelinating conditions.[30] A more recent review by the IOM reported only anaphylaxis in some individuals that could be linked to vaccine. For most conditions reviewed, the evidence was inadequate to accept or reject a causal relationship.[119] Recombinant hepatitis B vaccine is contraindicated in persons with hypersensitivity to yeast. Immunization is not effective in eliminating the carrier state, but there is no known risk for vaccinating individuals who are carriers or who are already immune.[15]

In February 2018, ACIP recommended use of the new single-antigen recombinant hepatitis B vaccine with a novel cytosine-phosphate-guanine 1018 oligodeoxynucleotide adjuvant (Heplisav-B) for prevention of HBV infection in adults aged ≥18 years.[12] Approved by the FDA in November 2017, Heplisav-B is routinely administered in two doses given ≥4 weeks apart. It can be used as a substitute in a three-dose series with a different hepatitis B vaccine, but a valid two-dose series requires two doses of Heplisav-B with ≥4 weeks between doses. When feasible, a vaccine from the same manufacturer should be used to complete the vaccination series. However, vaccination should not be deferred if the previously administered hepatitis B vaccine is unknown or if a vaccine from the same manufacturer is not available. A pregnant woman with an indication for hepatitis B vaccination should not receive Heplisav-B because no safety data are available on its use during pregnancy.

Human Papillomavirus Vaccines

Three HPV vaccines were developed using L1 capsid proteins, which self-assemble into VLPs that are similar in conformation to the natural virus.[117,120] All three are produced using recombinant techniques, which incorporate the gene expressing L1 into *Saccharomyces cerevisiae* or baculovirus-infected insect cells. Only one licensed vaccine is currently available in the United States: nona(nine)valent vaccine (9vHPV) containing types 6, 11, 16, 18, 31, 33, 45, 52, and 58. Types 16 through 58 in the vaccine cause about 80% of cervical cancers worldwide; types 6 and 11 cause about 90% of genital warts. Quadrivalent (types 6, 11, 16, and 18) HPV vaccine (4vHPV) and bivalent HPV vaccine (2vHPV), which contains types 16 and 18, are no longer available in the United States. The nonavalent vaccine is produced in yeast and contains an aluminum hydroxide adjuvant.

For efficacy studies for 4vHPV, a combined analysis of four clinical trials evaluating high-grade lesions (cervical intraepithelial neoplasia grade 2 or 3 [CIN 2/3] or adenocarcinoma in situ [AIS]) associated with types 16 and 18 revealed an efficacy of 100% with a lower bound of the 95% confidence limit of 92.9%. Effectiveness against genital warts related to any of the four types was 98.9% (95% confidence interval [CI], 93.7%–100%). The duration of protection is unknown, but with over 10 years of data, there is no evidence of waning protection. Efficacy of 4vHPV in males has been demonstrated for prevention of genital warts, anal intraepithelial neoplasia types 2/3 and anal intraepithelial neoplasia types 1/2/3 (88%–89%, 78%, and 75%, respectively).[121,122]

9vHPV has been shown to have similar immunogenicity to 4vHPV for the four shared types, and is approximately 95% effective against the five additional HPV types in the vaccine.

Local reactions were more common in vaccine recipients. After licensure, concerns were raised about serious adverse events temporally related to HPV vaccine, such as seizures and autoimmune disorders, but the postlicensure studies have not found an elevated risk.[122a]

Within 4 years of use of these vaccines, vaccine type prevalence of HPVs decreased from 11.5% to 5.1% among females 14 to 19 years of age.[123] ACIP recommends routine HPV vaccination at age 11 or 12 years. The vaccination schedule can be started at age 9 years. ACIP also recommends vaccination for females aged 13 to 26 years, for males aged 13 to 21 years who were not vaccinated previously, and for males to 26 years of age if they are immunosuppressed, have HIV infection, or are MSM. Vaccine also may be administered to all men 22 years to 26 years of age.

In December 2016, ACIP recommended that a two-dose schedule would be sufficient for girls and boys who initiate the vaccination series at ages 9 through 14 years. The two doses should be administered with 6 to 12 months between the doses. Three doses at 0, 1 to 2 months, and 6 months remain recommended for persons who initiate vaccination at ages 15 through 26 years, for immunocompromised persons, and for people with sickle cell disease.[124]

Influenza Virus Hemagglutinin Vaccines–Inactivated and Recombinant (IIV and RIV)

Most inactivated influenza virus vaccines are manufactured in chicken eggs and are composed of inactivated disrupted ("split") influenza viruses or of purified surface antigens. Inactivated influenza vaccine (trivalent) or IIV3 contains antigens for two influenza A viruses, H1N1 and H3N2,

and one influenza B virus. Most IIV3 is administered intramuscularly; a preparation that is administered intradermally and approved for persons 18 years to 64 years of age was licensed in 2011. The intradermal IIV was changed from a trivalent to a quadrivalent vaccine a few seasons before it was discontinued (it was not marketed in 2018). One formulation of IIV3 contains four times the antigenic content of the others and is considered "high dose," and is an option for persons aged 65 years or older. Also an option for persons aged 65 years or older is an adjuvanted vaccine, which is an IIV3 vaccine that contains a squalene-based oil-in-water emulsion.

Starting in the 2013–14 influenza season, some vaccines included antigens from two influenza A virus subtypes and two influenza B virus lineages, Yamagata and Victoria, making them quadrivalent vaccines (IIV4). Quadrivalent vaccine is an option, but there is no preference for its use in any group.

There are two forms of IIVs that are not manufactured in eggs. Cell-cultured–based influenza vaccine (ccIIV4) is manufactured in Madin-Darby canine kidney cells, is quadrivalent, is intramuscularly administered, and has been approved for use in persons 4 years of age or older. Quadrivalent recombinant hemagglutinin influenza vaccine (RIV4) is manufactured through reverse genetics in an insect cell line to produce influenza antigen and never uses the entire influenza virus. RIV4 and ccIIV4 avoid use of eggs for manufacture, which would make their production sustainable even if there were a shortage of eggs, as could occur in a pandemic. ccIIV4 uses seed virus that is isolated in eggs and therefore is not considered egg free, although the remaining quantity of egg protein is extremely low. RIV4 is considered egg free.[6]

Because of the frequent antigenic changes in influenza viruses, the antigenic content of influenza virus vaccines may be changed annually to reflect the influenza A and B virus strains in circulation. In most years, at least one of the strains is different from the preceding year's vaccine. The efficacy of the vaccine in protecting against influenza is related to the age of the person immunized and to the degree of concordance between the virus strains included in the vaccine and the strains that are circulating in the community. When periodic changes in the antigenic structure of circulating influenza viruses occur, vaccine that contains antigens representative of prior viruses has decreased or no effectiveness. In recent years, influenza vaccine effectiveness has been approximately 40% to 60% when there is a good match between strains in the vaccine and circulating strains (across all age groups).[125] Influenza vaccine has been estimated to be about 60% effective in preventing influenza in healthy adults younger than 65 years, when there is a good match.[126,127]

In nursing home settings, effectiveness has often been substantially lower, approximately 20% to 40%.[128] Some studies show higher effectiveness for preventing complications of influenza in such settings—for instance, 50% to 60% in preventing hospitalization or pneumonia and 80% in preventing death; however, such studies may be biased if healthier persons are more likely to be vaccinated than those who are less healthy.[128] Influenza vaccination might reduce the frequency of secondary complications and might reduce the risk for influenza-related hospitalization and death among community-dwelling adults aged 65 years or older with and without high-risk medical conditions.[129–131] Preliminary estimates of effectiveness of the A/H3N2 component of the 2017–18 vaccine showed about 17% effectiveness in the elderly, compared with 10% to 37% in younger adults. In contrast, effectiveness against influenza B strains was substantially higher in all age groups in that season: 29% to 57% effective in all age groups.[132] Efficacy data among young children are limited. A meta-analysis of five studies showed efficacy of 59% in children 6 months to 15 years of age.[133] In 2010, ACIP recommended that all persons aged 6 months or older be vaccinated annually.[6] This should provide individual benefits to those who are vaccinated but also has the potential to reduce community transmission of the virus and provide indirect benefit to others.

Although routine annual influenza vaccination is recommended for all persons 6 months or older, when vaccine supply is limited, vaccination efforts should focus on delivering vaccination to the following persons (no hierarchy is implied by order of listing): all children aged 6 months to 59 months; all persons aged 50 years or older; adults and children who have chronic pulmonary (including asthma) or cardiovascular (except isolated hypertension), renal, hepatic, neurologic, hematologic, or metabolic disorders (including diabetes mellitus); persons who have immunosuppression (including immunosuppression caused by medications or by HIV infection); women who are or will be pregnant during the influenza season; children and adolescents (aged 6 months to 18 years) who are receiving aspirin or salicylate-containing medications and who might be at risk for experiencing Reye syndrome after influenza virus infection; residents of nursing homes and other long-term care facilities; American Indians/Alaska Natives; and persons who are extremely obese (body mass index ≥40). Influenza vaccination should also be emphasized for health care personnel; household contacts and caregivers of children aged 5 years or younger and adults aged 50 years or older, with particular emphasis on vaccinating contacts of children younger than 6 months; and household contacts and caregivers of persons with medical conditions that put them at higher risk for severe complications from influenza.

For the 2018–19 season, it was recommended that children 6 months to 8 years of age being vaccinated for the first time receive two doses of vaccine with an interval of at least 4 weeks between them. Children who had received two total doses or more of trivalent or quadrivalent vaccine before July 1, 2018 required only one dose of the 2018–19 recommended vaccine.[134] Influenza seasons can peak anywhere from November to May, although the peak most often occurs in January or later, February being the most common month. Thus, although October and November have been the traditional months for influenza vaccination, during many influenza seasons vaccination through February, and even March, will provide benefit.

Adverse events associated with current influenza vaccines are infrequent. During the swine influenza immunization program of 1976, an elevated incidence rate of Guillain-Barré syndrome (GBS) was noted in recipients of the swine influenza vaccine.[135] However, studies during the 1992–93 and 1993–94 influenza seasons suggested that influenza vaccines may have been associated with GBS at an attributable risk of about one additional case per 1 million doses in those years.[136] No cases of GBS within 6 weeks of vaccination were detected in persons 18 to 44 years of age, despite administration of about 4 million doses of vaccine over the two influenza seasons studied.[136]

If GBS is ever caused by current influenza vaccines, this is a rare occurrence. In contrast, the risk for hospitalization from influenza disease and its complications is orders of magnitude higher in most populations in which vaccine is recommended. Given the substantial benefits of influenza vaccine among the targeted populations, risk for GBS, if any, is exceeded by benefits. Several studies have shown an increased risk, but results were variable within and across studies and subject to methodologic challenges due to narcolepsy epidemiology and increased awareness about the association.[137–140]

An increased incidence of narcolepsy has been reported in those younger than 30 to 40 years who received adjuvanted (AS03) monovalent 2009 pandemic H1N1 vaccines used in Europe in 2009 and 2010, but this vaccine was not licensed in the United States.[141–144]

A recent Vaccine Safety Datalink (VSD) study found that women vaccinated early in pregnancy with an influenza vaccine containing the A(H1N1) 2009 strain and who also had been vaccinated the prior season with an A(H1N1)pdm09-containing influenza vaccine had an increased risk of spontaneous abortion (miscarriage) in the 28 days after vaccination.[145] Earlier studies did not find a link between influenza vaccination and miscarriage. This study examined data from a small number of women in a subgroup who received H1N1-containing vaccines in consecutive years. The small numbers in the study could have led to imprecise results.There is an ongoing investigation to study this issue further among women who were pregnant and eligible to receive influenza vaccine during the 2012–13 through 2014–15 influenza seasons. Results are anticipated in late 2018 or 2019.

Because pregnant women are at high risk of serious influenza complications, it is recommended that they receive influenza vaccination during any trimester of their pregnancy. Providers should consult current guidelines for more detailed and updated recommendations.

Data demonstrating the safety of IIV for HIV-infected persons are limited, but no evidence exists that vaccination has a clinically important impact on HIV infection or immunocompetence. It is especially important

to vaccinate HIV-infected persons because of their increased risk of influenza complications.

Live-Attenuated Influenza Vaccine

In 2003 the FDA licensed LAIV vaccine to be administered intranasally. Each viral strain in the vaccine consists of six internal genes from a cold-adapted, temperature-sensitive, attenuated mutant.[6,146,147] The hemagglutinin and neuraminidase are derived from circulating wild strains. The cold adaptation is supportive of growth of the vaccine viruses in the upper airways, and temperature sensitivity decreases their growth in the lower airways. The vaccine had been trivalent, with reassortants for each of the major circulating influenza viruses: A(H3N2), A(H1N1), and B. Since the 2013–14 season, the only LAIV preparation has been quadrivalent, including representative strains of the two influenza B lineages, Yamagata and Victoria.

A meta-analysis of five studies showed a pooled efficacy of 83% for LAIV in children 6 months to 7 years old prior to the 2012–13 season.[126] In a study of healthy children, vaccine was 94% effective after two doses in children 60 to 71 months of age in 1996–97, with a good match between vaccine and circulating wild virus, and 86% in 60- to 84-month-old children in 1997–98, when vaccine and circulating strains substantially diverged. In addition, vaccine reduced influenza A–associated febrile otitis media (vaccine efficacy, 94%).[6] Estimated efficacy of LAIV against laboratory-confirmed influenza in randomized, placebo-controlled studies among 18- to 49-year-old adults was 36% in the 2007–08 season but was not significantly different from zero in either the 2004–05 or the 2005–06 season.[6]

For the 2016–17 seasons, as well as for the 2017–18 seasons, ACIP recommended that LAIV4 not be used, because of concerns regarding low effectiveness against influenza A(H1N1)2009 in the United States during the 2013–14 and 2015–16 seasons.[134] In the 2014–15 season, the effectiveness of LAIV4 among 2- to 8-year-olds was found to be 3% against the H3N2 strain.[148] In the 2015–16 season the effectiveness of LAIV among 2- to 17-year-olds was found to be 5%, and against the H1N1 strain was found to be −19%.[149] This recommendation to not use LAIV4 continued through the 2017–18 seasons. Previous data and recommendations regarding the use of LAIV are further discussed in the following text and in Chapter 165.

In adults 18 through 49 years of age, solicited adverse reactions occurring in at least 1% of LAIV4 recipients and at a higher rate (≥1% rate difference after rounding) compared with placebo include runny nose (44% LAIV4 vs. 27% placebo), headache (40% LAIV4 vs. 38% placebo), sore throat (28% LAIV4 vs. 17% placebo), tiredness or weakness (26% LAIV4 vs. 22% placebo), muscle aches (17% LAIV4 vs. 15% placebo), cough (14% LAIV4 vs. 11% placebo), and chills (9% LAIV4 vs. 6% placebo).[150–152]

Contraindications to LAIV include a history of severe allergic reaction to any component of the vaccine or after a previous dose of any influenza vaccine; concomitant aspirin or salicylate-containing therapy in children and adolescents; 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 that during the preceding 12 months their child had wheezing or asthma or whose medical record indicates a wheezing episode has occurred during the previous 12 months; children and adults who are immunocompromised from any cause (including immunosuppression caused by medication or by HIV infection); close contacts and caregivers of severely immunosuppressed persons who require a protected environment; pregnancy; and receipt of an influenza antiviral medication within the previous 48 hours. Precautions regarding use of LAIV include moderate or severe acute illness or fever; history of GBS within 6 weeks of a previous dose of influenza vaccine; asthma in persons aged 5 years and older; and other underlying medical conditions that might predispose to complications after wild-type influenza infection (e.g., chronic pulmonary, cardiovascular [except isolated hypertension], renal, hepatic, neurologic, hematologic, or metabolic [including diabetes mellitus] disorders).[6]

Although there had been promise that LAIV would be highly effective based on prelicensure trials and early experience, the consistent poor effectiveness documented in the United States starting in the 2013–14 influenza season, particularly against H1N1 viruses, led ACIP to recommend the vaccine not be used through 2017–18. Recent data led to the recommendation that LAIV is an option for influenza vaccination of those in whom it is appropriate to use LAIV in 2018–19.[134]

Persons with a history of egg allergy who have experienced only hives after exposure to eggs should receive influenza vaccine. Any licensed and recommended influenza vaccine (i.e., any age-appropriate IIV, RIV4, or LAIV4) that is otherwise appropriate for the recipient's age and health status may be used.

Persons who report having had reactions to egg involving symptoms other than hives, such as angioedema, respiratory distress, lightheadedness, or recurrent emesis, or who required epinephrine or another emergency medical intervention, may similarly receive any licensed and recommended influenza vaccine (i.e., any age-appropriate IIV, RIV4, or LAIV4) that is otherwise appropriate for the recipient's age and health status. 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 conditions.

Japanese Encephalitis

In 2009, inactivated Vero (green monkey kidney) cell culture–derived Japanese encephalitis (JE) vaccine (JE-VC; Ixiaro [Intercell Biomedical, Livingston, United Kingdom]) was licensed for use in persons aged 17 years or older and subsequently was recommended for travelers in this age group at high risk of JE. This is the only JE vaccine that is licensed and available in the United States. In May 2013 the FDA extended the indication for use of JE-VC to include children 2 months to 16 years of age, and subsequently ACIP extended recommendations for use in this age group. The vaccine was licensed in the United States based on a noninferiority immunogenicity study comparing neutralizing antibodies elicited by the new vaccine with the previously available JE vaccine grown in mouse brains ([JE-MB]-[JE-VAX]). The JE-MB vaccine was associated with hypersensitivity and neurologic adverse reactions. Fewer vaccine-associated hypersensitivity or neurologic adverse events are expected to occur after use of JE-VC compared with the previously used JE-MB vaccine. JE-VC vaccine consists of purified, inactivated JE proteins derived from attenuated virus propagated in Vero cells. Immunogenicity studies have demonstrated noninferiority to the JE-MB vaccine, which was proved to be 91% effective in a large-scale trial in Thailand.[153] JE-VC vaccine is recommended for travelers who plan to spend a month or longer in endemic areas during the Japanese encephalitis virus (JEV) transmission season. This includes long-term travelers, recurrent travelers, or expatriates who will be based in urban areas but are likely to visit endemic rural or agricultural areas during a high-risk period of JEV transmission. Vaccine should also be considered for the following: short-term (less than 1 month) travelers to endemic areas during the JEV transmission season, if they plan to travel outside an urban area and their activities will increase the risk of JEV exposure; travelers to an area with an ongoing JEV outbreak; and travelers to endemic areas who are uncertain of specific destinations, activities, or duration of travel. The immunization schedule is two doses administered 28 days apart.[154,155]

Measles-Containing Vaccine

Measles vaccine is a live-attenuated virus vaccine recommended for use in all children 12 months and older who do not have contraindications.[156] When administered to a child 12 to 15 months or older, the median one-dose efficacy is 93% and the median two-dose efficacy is 97%.[157] Only a single dose is needed to provide long-lasting, probably lifelong, immunity in those who respond to the vaccine. However, evidence indicates that measles transmission can be sustained among the 2% to 5% of vaccinated persons who fail to be protected after an initial dose of vaccine. Therefore, beginning in 1989 a two-dose schedule of measles-containing vaccine was recommended in the United States. The first dose should be administered at 12 to 15 months of age. Lower levels of maternal antibody from currently vaccinated mothers allow higher rates of seroconversion at 12 months than in the past, when most maternal antibody came from mothers with naturally acquired disease.[158]

The second dose should be administered 1 month or more after the first dose, typically at entry to school (4–6 years of age). Both doses should routinely be given as combined MMR vaccine or MMR and varicella (MMRV).[156,159] Both MMR and MMRV vaccines are associated with an elevated febrile seizure risk, but data suggest that MMRV, because it is associated with a higher risk for fever than the separate administration of MMR and varicella, also may be associated with an increased risk for febrile seizures compared with simultaneous separate MMR and varicella vaccines after the first dose of the two-dose series.[159] In June 2009, after consideration of the postlicensure data and other evidence, ACIP adopted new recommendations regarding use of MMRV vaccine for the first and second doses and identified a personal or family (i.e., sibling or parent) history of seizure as a precaution for use of MMRV vaccine. For the first dose of measles, mumps, rubella, and varicella vaccines at age 12 to 47 months, either MMR vaccine and varicella vaccine or MMRV vaccine may be used. Providers who are considering administering MMRV vaccine should discuss the benefits and risks of both vaccination options with the parents or caregivers. Unless the parent or caregiver expresses a preference for MMRV vaccine, ACIP recommends that MMR vaccine and varicella vaccine should be administered separately for the first dose in this age group. For the second dose of measles, mumps, rubella, and varicella vaccines at any age (15 months through 12 years—the age for which the vaccine is approved) and for the first dose at age 48 months or older, use of MMRV vaccine generally is preferred over separate injections of its equivalent component vaccines (i.e., MMR vaccine and varicella vaccine). Recent data from Australia suggest that MMRV is not associated with an increased risk of febrile seizures when it is the second dose of an MMR-containing vaccine.[160]

All college entrants who have not received two doses of MMR vaccine on or after their first birthday should receive two doses.[156] The two doses can be given separated by 1 month. Immunization is recommended for all people not known to be immune. Because people born before 1957 are likely to have been infected naturally, they usually are considered immune. Other acceptable evidence of measles immunity is documentation of adequate vaccination or laboratory evidence of immunity to measles.[157] Health care facilities should consider recommending a dose of MMR to unvaccinated providers born before 1957 who do not have laboratory evidence of immunity to both measles and rubella or other acceptable evidence of measles immunity.

Because measles is much more prevalent outside the United States, adequate vaccination is recommended for all travelers born after 1956. These travelers should have evidence of having received two doses.[156] Infants 6 months to 11 months of age should receive a dose of MMR vaccine if they travel internationally. One dose is recommended for travel in this age group, but this dose is not considered part of the routine two-dose childhood series (beginning at 12 months of age), so two additional doses should be administered at the appropriate age.[157]

Adverse reactions associated with measles vaccine include fever of 39.4°C or greater in 5% of recipients and transient rashes in about 5% of vaccinees.[157] Because measles vaccine can cause fever, it can be associated with febrile seizures.[161] Children with prior personal histories of seizures or histories of seizures in the immediate family may be at increased risk for febrile seizures after MMR vaccination.[162] Anaphylaxis and thrombocytopenic purpura also appear to be caused rarely by MMR.[65] Encephalopathy with onset about 10 days after vaccination has been reported in vaccine recipients, with a frequency of approximately 1 in 2 million vaccinations; although a causal role for measles vaccine has not been established.[163] There is no association between MMR vaccine and autism.[67,164]

Measles vaccine is contraindicated for pregnant women and in persons who are immunocompromised because of either congenital or acquired disorders (e.g., leukemia or immunosuppressive drugs), with the exception of persons infected with HIV. Because measles may cause severe disease in HIV-infected people, MMR vaccine is recommended for persons who do not have evidence of severe immunosuppression. Absence of severe immunosuppression is defined as CD4 percentages greater than or equal to 15% for 6 months, or longer for persons 5 years old or younger, and CD4 percentages greater than or equal to 15% and CD4 count greater than or equal to 200 lymphocytes/mm^3 for 6 months, or longer for persons older than 5 years. When only CD4 counts or CD4 percentages are available for those older than 5 years, the assessment of severe immunosuppression can be on the basis of CD4 values that are available. When CD4 percentage is not available for children 5 years old or younger, the assessment of severe immunosuppression can be on the basis of age-specific CD4 counts at the time the CD4 counts were measured (i.e., absence of severe immunosuppression is defined as 6 months' duration above age-specific CD4 count criteria: CD4 count greater than 750 lymphocytes/mm^3 in those 12 months old or younger and CD4 count greater than or equal to 500 lymphocytes/mm^3 in those 1–5 years of age).[157]

Meningococcal Vaccines

Four meningococcal containing vaccines are available in the United States.[165] Two vaccines contain purified meningococcal capsular polysaccharides of groups A, C, Y, and W, conjugated to protein (MenACWY), which results in a vaccine that is immunogenic in infants and young children. Immunization involves induction of T-lymphocyte cell-dependent responses, and induces immunologic memory to meningococcal polysaccharide.[27,166,167] Two vaccines are serogroup B meningococcal (MenB) recombinant protein vaccines. MPSV is no longer available in the United States.

Conjugate meningococcal vaccines reduce carriage and induce herd protection.

One conjugate vaccine, MenACWY-D (Menactra), is licensed for persons 9 months to 55 years of age, and the other conjugate vaccine, MenACWY-CRM (Menveo), is licensed for persons 2 months to 55 years of age. The antibody responses to each of the four conjugated polysaccharides included in each of the quadrivalent vaccines are serogroup specific, independent, and comparable for the two vaccines. Meningococcal conjugate vaccines routinely are indicated for immunization of adolescents, for control of outbreaks attributable to a vaccine serogroup, and for use among certain high-risk groups, such as persons with persistent complement component deficiencies, eculizumab use, HIV infection, or anatomic or functional asplenia, and laboratory personnel who routinely are exposed to isolates of *N. meningitidis*. Meningococcal conjugate vaccine (MenACWY) routinely is recommended for all adolescents beginning at 11 to 12 years of age, with a booster dose at 16 years of age. Adolescents who receive their first dose of MenACWY at 11 to 12 years of age routinely are recommended for a booster at 16 years of age. Adolescents who receive their first dose of vaccine at 13 to 15 years of age are recommended to receive a booster at 16 to 18 years of age. First-year college students 19 years of age or older living in residence halls should receive a dose if they have not been vaccinated after the 16th birthday. Regardless of attendance in a college, if a high-risk scenario develops (e.g., travel to a region in the "the meningitis belt" of sub-Saharan Africa [which stretches from Senegal to Ethiopia], entering the military, routine exposure to *N. meningitidis* through microbiology laboratory work), a dose should be provided if it has been 5 years since the most recent dose. Children traveling to the meningitis belt (or to the Hajj in Saudi Arabia) should receive a quadrivalent meningococcal conjugate vaccine (MenACWY-CRM or MenACWY-D).

When initiated at 2 months of age, a four-dose schedule is recommended for MenACWY-CRM, with doses at 2, 4, 6, and 12 months of age; when initiated at 9 to 23 months of age, a two-dose schedule is recommended. Children aged 9 months and older can receive MenACWY-CRM or MenACWY-D. MenACWY-D is recommended as a two-dose primary series, with 3 months separating the doses (8 weeks minimum). Children 2 to 23 months of age with functional or anatomic asplenia or HIV infection should receive MenACWY-CRM vaccine. To avoid interference with the immunologic response to the infant series of PCV13, children younger than 24 months with functional or anatomic asplenia or HIV infection should not receive MenACWY-D vaccine. In contrast, MenACWY-CRM does not demonstrate immune interference with PCV7 (and, by extrapolation, PCV13) after the 12-month dose, and can therefore be administered concomitantly with PCV13. Because a potential for immunologic interference with MenACWY-D response has been demonstrated when MenACWY-D is administered 30 days after DTaP vaccine, it is recommended that

MenACWY-D be given either before or concomitantly with DTaP in children at increased risk for meningococcal disease.

Adults at increased risk for meningococcal disease (functional or anatomic asplenia, complement component deficiency, travel or residence in the meningococcal belt, exposed to an outbreak of vaccine serogroup) also should receive either MenACWY-D or MenACWY-CRM. A two-dose primary series is recommended for adults with functional or anatomic asplenia, HIV infection, and complement deficiency.

For children first vaccinated before 7 years of age with MenACWY, revaccination should be considered after 3 years if they remain at high risk, and then every 5 years thereafter for subsequent booster doses, as long as they remain at high risk.[60]

The development of vaccines against meningococcus serogroup B has been hampered because the serogroup B polysaccharide is very poorly immunogenic in humans. Through the use of reverse genetics, recombinant serogroup B antigens that can provide protection against serogroup B have been identified, and two vaccines were licensed in the United States in 2014 and 2015, respectively: MenB-FHbp (Trumenba) and MenB-4C (Bexsero). ACIP recommended that the vaccines be used to immunize individuals aged 10 years or older who are at increased risk for serogroup B disease (persistent complement component deficiencies, eculizumab use, anatomic or functional asplenia, or at risk because of an outbreak of serogroup B disease).[169] While ACIP does not routinely recommend a serogroup B meningococcal vaccine for all teens and young adults without risk factors for serogroup B disease, all teens and young adults may get vaccinated, preferably at 16 through 18 years old; this decision is left to individual consideration of health care providers, parents, and patients.[172] For adults at increased risk for meningococcal disease and for use during serogroup B meningococcal disease outbreaks, three doses of MenB-FHbp should be administered at 0, 1 to 2, and 6 months. When given to healthy adolescents and young adults who are not at increased risk for meningococcal disease, two doses of MenB-FHbp should be administered at 0 and 6 months. The other MenB vaccine, Men-4C, is a two-dose series, with the two doses administered at least a month apart. (see Fig. 316.4).

Mumps Vaccine

Mumps vaccine is a live-attenuated virus vaccine that is recommended for use in all children aged 12 months or older who do not have contraindications. Mumps vaccine is administered routinely as MMR or MMRV at 12 to 15 months of age.[171] When administered on or after the first birthday, 49% to 91% of recipients can be expected to acquire protection. Although protection had been thought to be lifelong, investigations after resurgences of mumps in 2006, 2009–10, and 2016 suggested that some persons may lose immunity over time.[172] A second dose is recommended with MMR or MMRV, usually at 4 to 6 years of age.[171] As with measles, most persons born before 1957 are likely to have been infected naturally with mumps virus and generally can be considered immune; otherwise, individuals should be considered susceptible unless they have documentation of having received one or two doses of live mumps vaccine (depending on age), laboratory evidence of mumps immunity, or laboratory evidence of mumps disease. These three factors are considered presumptive evidence of immunity.[171] For health care personnel, acceptable evidence of immunity consists of laboratory documentation of immunity, laboratory documentation of disease, or written documentation of two doses of mumps-containing vaccines, or laboratory evidence of mumps immunity.[157,173] Contraindications to mumps vaccine are pregnancy and an immunocompromised state (see "Measles-Containing Vaccine"). Persons with a history of anaphylactic reactions to eggs may be vaccinated. Adverse events associated with mumps vaccine are uncommon. Parotitis and orchitis have been reported rarely. Thrombocytopenic purpura and anaphylaxis appear to be caused rarely by MMR.[65] Aseptic meningitis has been associated with the Urabe and Leningrad-Zagreb strains of mumps vaccine, strains not available in the United States.[172,173] The Jeryl Lynn strain used in US vaccines has not been proved to cause aseptic meningitis.[65]

Persons previously vaccinated with two doses of a mumps virus–containing vaccine who are identified by public health authorities as being part of a group or population at increased risk for acquiring mumps because of an outbreak should receive a third dose of a mumps virus–containing vaccine to improve protection against mumps disease and related complications.[157,173,174] In an outbreak setting, persons vaccinated previously with one dose of mumps-containing vaccine who have been identified by public health officials as at increased risk of mumps because of the outbreak should receive a second dose of mumps-containing vaccine, even if they would not otherwise have a routine recommendation for a second dose of mumps-containing vaccine (https://www.cdc.gov/vaccines/pubs/surv-manual/chpt09-mumps.html). Everyone who is determined to be part of the group at increased risk for getting mumps should receive a dose of MMR vaccine. That includes people who do not have vaccine records that prove they received two doses of MMR vaccine. No additional dose is recommended for people who already received three or more doses before the outbreak.[175]

Pertussis-Containing Vaccine

Acellular pertussis vaccines are made from purified components of the organism *Bordetella pertussis* and detoxified pertussis toxin (PT); whole-cell pertussis vaccines, made from suspensions of killed whole *B. pertussis,* are no longer available in the United States, although they continue to be widely used internationally.[176] Acellular pertussis vaccines currently available in the United States contain pertussis toxoid, filamentous hemagglutinin (FHA), and pertactin (69-kDa protein). In addition, they may contain fimbriae.[55] Pertussis vaccines are combined with diphtheria and tetanus toxoids as DTaP (acellular pertussis vaccines for children) or Tdap (for adolescents and adults). Tdap contains reduced amounts of diphtheria toxoid and acellular vaccine components compared with DTaP vaccine for children. The primary immunizing course for children consists of three doses of DTaP administered intramuscularly at 4- to 8-week intervals, typically given at 2, 4, and 6 months of age. A fourth dose is given about 6 to 12 months later (15–18 months of age) and a fifth dose at 4 to 6 years of age. Acellular pertussis vaccines are preferred over whole-cell pertussis vaccines because the efficacy of acellular vaccines were thought to be comparable to whole-cell vaccines in prelicensure clinical trials, and because the incidence of adverse events after acellular vaccines is significantly lower than after whole-cell vaccines. As of July 2013, two acellular vaccines for children were available in the United States: Daptacel (Sanofi Pasteur, Swiftwater, PA), which contains PT, FHA, pertactin, and fimbriae types 2 and 3, and Infanrix (GlaxoSmithKline), which contains PT, FHA, and pertactin. The efficacy found for one of the old US whole-cell vaccines after three doses in clinical trials in Europe was 36% to 48%.[177,178] Point estimates of vaccine efficacy ranged from 80% to 85% for vaccines currently licensed in the United States.[179] Effectiveness varies with time from completion of a vaccine series.[180]

Local reactions occur about one-tenth to one-half as frequently with acellular vaccines as with whole-cell vaccines. For example, the incidence of erythema by the third evening after any of the first three doses of acellular vaccines for children ranged from 26.3% to 39.2% in one large comparative trial, compared with 72.7% in those who received the whole-cell vaccine. In that study, the incidence of fever (>39.4°C) after acellular vaccines was 3.3% to 5.2%, compared with 15.9% after receipt of whole-cell vaccine.[55] More serious adverse events, such as seizures and hypotonic hyporesponsive episodes, also appear to occur less frequently after acellular vaccines than after whole-cell vaccines.[181,182] The lower incidence of fever associated with acellular vaccines would be expected to decrease febrile seizures, especially after the fourth dose.

Contraindications to DTaP vaccines include an immediate anaphylactic reaction or encephalopathy not attributable to another identifiable cause within the 7 days after a prior dose. The following events are considered to be precautions specific to DTaP: (1) children with evolving neurologic disorders, who should have immunization deferred until the situation is clarified—once stable, they can receive pertussis vaccine[176]; (2) GBS less than 6 weeks after a previous dose of tetanus-toxoid vaccine; (3) history of Arthus-type hypersensitivity reactions after a previous dose of tetanus or diphtheria-containing vaccines—defer vaccination until at least 10 years have elapsed since the last tetanus-toxoid vaccine; and (4) severe or moderate acute illness with or without fever.

Given the benefits of vaccination, administration of pertussis vaccines to children with stable seizure disorders or with family histories of seizures is recommended in the United States.

Extensive swelling of the thigh or entire upper arm after the fourth or fifth doses of the DTaP series has been reported. The frequency appears to be 2% to 3%, and the pathogenesis is unclear. Extensive limb swelling is commonly misperceived as a contraindication for DTaP and/or Tdap.[176]

DTaP is available in four combination formulations: with inactivated polio and hepatitis B vaccines (Pediarix); with inactivated polio and Hib vaccines (Pentacel, Sanofi Pasteur); and with inactivated polio (Kinrix [GlaxoSmithKline] and Quadracel [Sanofi Pasteur]). Combinations of acellular vaccines with Hib have generally resulted in diminished antibody response to the Hib component when administered to infants.[96] However, the immune response to Hib in persons who receive Pentacel is considered adequate. Kinrix and Quadracel are licensed only for the fifth dose of DTaP, which is usually administered at the same time as the fourth dose of IPV at 4 to 6 years of age. Data are insufficient to document the safety, immunogenicity, and efficacy of use of DTaP vaccines from different manufacturers in a mixed sequence. For this reason, whenever feasible, the same brand of DTaP should be used for all doses in the vaccination series. However, if the type of vaccine previously administered is unknown or is not available, any of the available licensed DTaP vaccines can be used to complete the vaccination series.

Concerns about the safety of whole-cell pertussis vaccines have led to decreased vaccine coverage in some countries. Whole-cell pertussis vaccines have been implicated in encephalopathy, and these concerns persist even though there is some evidence that encephalopathy may have been due to a cause distinct from vaccines.[183] In the United Kingdom, pertussis vaccine uptake declined markedly in the period from 1974 to 1978. The result was a major epidemic of pertussis in the years 1977 to 1979, with a second epidemic in 1982. This experience and similar ones in Japan and other countries illustrate the necessity for maintaining protection against pertussis.[184]

Studies of pertussis epidemiology suggest that adults may play an important role in sustaining transmission.[178–192] Waning immunity in adolescence after receipt of the acellular DTaP vaccine in childhood has likely contributed to a resurgence of disease in adolescents and adults. Pertussis in adolescents and adults may account for increases in pertussis among infants too young to be protected through vaccination.[192]

During 2005, two acellular pertussis–containing vaccines were licensed as a single dose for administration to adolescents and adults. Both vaccines are combined with tetanus toxoid and reduced quantities of diphtheria toxoid (Tdap).[93] Adacel (Sanofi Pasteur) contains detoxified PT (2.5 μg), FHA (5 μg), pertactin (3 μg), and fimbriae types 2 and 3, similar to the pertussis components of Daptacel, the childhood preparation. The pertussis components of Boostrix (GlaxoSmithKline) consist of PT (8 μg), pertactin (2.5 μg), and FHA (8 μg), similar to the pertussis components of Infanrix, the childhood preparation. Both vaccines contain aluminum adjuvants. Neither vaccine contains thimerosal. The vaccines were licensed on the basis of inducing antibody responses to pertussis antigens similar in magnitude to the responses associated with early childhood vaccination, although efficacy was also demonstrated in adults with a vaccine similar to Boostrix.[193] The childhood vaccines proved to be effective in preventing pertussis.

Boostrix is licensed for administration to persons aged 10 years or older, whereas Adacel is licensed for persons 10 to 64 years of age. Tdap is indicated routinely as a booster for adolescents at 11 to 12 years of age in place of the previously recommended tetanus and diphtheria toxoids for adult use (Td). In addition, all persons older than 12 years should receive a single dose of Tdap, which can replace any of the decennial boosters of Td. When feasible, Boostrix, which is licensed for those 10 years old and older, should be used for persons aged 65 years or older.[194]

Tdap is not indicated for primary immunization. However, it can be used for any one of the doses in the primary series of Td for unimmunized adolescents and adults. It is now recommended that Tdap be administered to anyone aged 11 years and older without respect to previous interval from last tetanus toxoid-containing vaccine. Health care providers also should be vaccinated. Tdap is especially indicated for adults who have never received a prior Tdap booster and who will be caring for young infants, because such children are susceptible to pertussis before active immunity can be induced by DTaP. Vaccination is recommended in pregnancy as a way of reducing infant pertussis both through decreasing the risk for transmission of disease to the infant from the mother and through transfer of maternal antibodies against pertussis across the placenta.[195] Based on studies of antibody levels in cord blood from women vaccinated during pregnancy, Tdap should be administered to women who are pregnant and should be administered in every pregnancy, preferably during the early part of gestational weeks 27 through 36.[71] Studies of antibody levels in cord blood of infants born to mothers who may have been vaccinated as long as 2 years previously did not show appreciable antibody levels, suggesting that doses from previous pregnancies are unlikely to provide protection to the infants from subsequent pregnancies, and therefore a protective dose should be given during each pregnancy. Except for repeat doses recommended for each current pregnancy, only one dose of Tdap is recommended for adults because the duration of protection is short and the impact of repeat Tdap vaccination on disease burden is unclear.[71]

Plague Vaccine

Plague vaccine is no longer available in the United States. Killed whole-cell vaccines and live-attenuated vaccines are used elsewhere in the world, and new subunit and mucosal vaccines are under development.[196]

Pneumococcal Polysaccharide Vaccine

Pneumococcal polysaccharide vaccine initially was licensed as a purified preparation of 14 different serotypes of pneumococcal capsular polysaccharide in 1977. Since 1983, vaccine containing 23 types (PPSV23) has replaced the earlier version. The types included in the current vaccine and immunologically related types are responsible for about 60% to 75% of all bacteremic pneumococcal disease in the United States. Older versions of pneumococcal polysaccharide vaccine containing higher doses of antigens and targeting fewer serotypes were highly effective in reducing pneumococcal disease among South African gold miners (a group at particularly high risk) and among military recruits.[197–199] In populations at high risk for pneumococcal infections, such as elderly persons and patients with high-risk medical conditions, more recent formulations generally have been found to be effective against pneumococcal bacteremia and other types of invasive pneumococcal disease but not necessarily against nonbacteremic pneumococcal pneumonia. Studies of patients with isolates from normally sterile body fluids have generally reported efficacies of 50% to 80% overall, with lower efficacy in persons who have compromised immune systems.[200–203] A study of Navajo adults did not demonstrate efficacy against invasive pneumococcal disease in this high-risk population.[204] The vaccine is licensed for persons aged 2 years or older. The schedule and indicated uses of pneumococcal polysaccharide vaccine are highlighted in the ACIP-recommended immunization schedule for children and adolescents aged 18 years or younger and the recommended immunization schedule for adults aged 19 years or older, United States[205] (see Figs. 316.1A and 316.2).

PPSV23 is recommended for adults and children 2 years old and older at increased risk for pneumococcal diseases including those with chronic heart, lung, or liver disease; diabetes mellitus; cerebrospinal fluid (CSF) leak; cochlear implants; sickle cell disease or other hemoglobinopathies; congenital or acquired asplenia or splenic dysfunction; HIV infection; chronic renal failure or nephrotic syndrome; congenital immunodeficiency; generalized malignancy; multiple myeloma; iatrogenic immunosuppression; alcoholism; or cigarette smoking. PPSV23 is also recommended for healthy elderly persons (≥65 years of age).[206] Starting in August 2014, ACIP recommended that PCV13 be administered in series with PPSV23 in individuals aged 65 years and older[207] (see later).

Polysaccharide vaccines are not effective in children younger than 2 years. Children who have completed the PCV series before age 2 years and who are in these high-risk groups should receive one dose of pneumococcal polysaccharide vaccine at age 2 years.[208]

A single dose is administered by means of IM or subcutaneous injection. A single revaccination is recommended for persons aged 65 years or older who received an initial vaccination before age 65 years,

if at least 5 years have elapsed since that dose. A revaccination dose is also recommended for persons younger than 65 years with anatomic or functional asplenia or those who are immunocompromised, including patients with chronic renal failure and nephrotic syndrome. This dose should be administered after a minimum 5-year interval. If this second dose is administered before the 65th birthday, a third and final dose is recommended after the 65th birthday.

Pneumococcal Conjugate Vaccine

PCVs in which pneumococcal capsular polysaccharide is covalently linked to protein carriers have been developed. A 7-valent conjugate vaccine covalently linked to CRM protein (PCV7; Prevnar; Wyeth Lederle Vaccines, St. David's, PA) was first licensed for use in infants and young children in 2000. The seven polysaccharide types included in the licensed vaccine accounted for 80% of invasive infections in children younger than 6 years in the United States at the time of vaccine introduction.[208] In a prelicensure efficacy trial in northern California, the efficacy of the conjugate vaccine was 97% against invasive disease caused by serotypes in the vaccine.[209] The vaccine was also effective in prevention of pneumonia, with the greatest impact in the first year of life, with a 32% reduction,[209] and in prevention of acute otitis media caused by pneumococcal serotypes included in the vaccine.[210] Efficacy against invasive pneumococcal disease has been demonstrated in Native American children, a population at increased risk for disease.[210]

In February 2010, a 13-valent PCV with polysaccharides linked to CRM was licensed in children, and contains the 7 serotypes in PCV7 with 6 additional serotypes. Among infants receiving the three-dose primary infant series, responses to 10 of the PCV13 serotypes met the prespecified primary end-point criterion (percentage of subjects achieving an IgG seroresponse of ≥0.35 μg/mL 1 month after the third dose). Responses to serotypes 6B and 9V (contained in both vaccines) and new serotype 3 (only contained in PCV13) did not meet this criterion. For serotypes 6B and 9V, however, the differences were small.[211]

PCV is administered as a four-dose series, with doses at 2, 4, and 6 months of age, followed by a booster dose at 12 to 15 months of age.[210] The vaccine is recommended for all children younger than 2 years, and children 24 to 59 months of age. Healthy children 24 to 59 months of age who have not been vaccinated or completed the recommended schedule should receive one dose.[212] Children 24 to 59 months of age who have received an incomplete series of fewer than three doses before 24 months of age, and who have high-risk conditions such as chronic cardiac or pulmonary disease, diabetes mellitus, chronic liver disease, immunosuppression, renal failure or nephrotic syndrome, functional or anatomic asplenia, CSF leak, or cochlear implants should receive two doses of PCV13 vaccine.[206,208,213]

Widespread use of the conjugate vaccine has resulted in dramatic decreases in disease incidence among young children for whom the vaccine is recommended. In addition, decreases in disease incidence have also been observed among adults, probably as a result of decreased transmission of pneumococci from children to adults.[214] Decreases in disease are not restricted to invasive pneumococcal disease, but have also occurred in noninvasive pneumonia.[215] Surveillance of pneumococcal disease to date has revealed some evidence of serotype replacement by serotypes not contained in the vaccine, but such replacement has been far outweighed by the reduction in disease caused by serotypes in the vaccine.[215–217]

PCV was licensed for adults aged 50 years and older in 2011 and is now recommended for all adults with immunosuppression, including renal failure and nephrotic syndrome, functional or anatomic asplenia, CSF leak, or cochlear implants because of their increased risk of disease.[218] It is recommended that adults with these risk factors also receive at least one dose of PPSV23. They should receive PCV13 first, followed by a dose of PPSV23 8 weeks later. If an adult has received a dose of PPSV23, administering the dose of PCV13 that follows should be after an interval of 1 year to optimize the response to the dose of PCV13, which is affected by the previous dose of PPSV23. In August 2014, ACIP recommended that PCV13 be administered to individuals aged 65 years and older in series with PPSV23.[207] This decision was in part based on results of the placebo-controlled CAPiTA trial of PCV13 in 85,000 adults aged 65 years and older with no prior pneumococcal vaccination history. The CAPiTA trial demonstrated an efficacy of 45.6% against vaccine-type pneumococcal pneumonia, including both invasive pneumococcal disease and nonbacteremic pneumococcal pneumonia.[219] PCV13 should be administered first, followed by PPSV23 in individuals aged 65 years and older who have never received pneumococcal immunization. In healthy adults or high-risk immunocompetent adults, the interval between PCV13 and PPSV23 should be 1 year. The timing and regimen for those who have already received PPSV23 was described by the CDC in 2014[207] and 2015.[220]

In 2015, ACIP issued a summary of revised spacing rules for PCV13 and PPSV23 when both vaccines are recommended.[220] ACIP recommends that all adults aged 65 years or older who have not received pneumococcal vaccine and persons aged 2 years or older who are at high risk for pneumococcal disease should receive a dose of PCV13, followed by a dose of PPSV23.[220] The intervals between doses differ according to age and indication[220] and are described in Figs. 316.3 and 316.4.

Polio Vaccine

Although two types of polio vaccine are available in the world to control polio, live-attenuated oral polio vaccine (OPV) and injectable IPV, only IPV is currently available in the United States. The schedule consists of four doses of IPV at 2 months, 4 months, 6 to 18 months, and 4 to 6 years. The final dose should be administered at age 4 years and older regardless of the number of previous doses and at least 6 months after the previous dose.[221] IPV is available as a single vaccine or in combination with DTaP and hepatitis B vaccines (Pediarix), DTaP and Hib vaccines (Pentacel), or DTaP alone (Kinrix and Quadracel). Although Pediarix can be used for the first three doses of IPV at 2, 4, and 6 months, single IPV or DTaP/IPV is needed for the fourth dose. Pentacel can be used for any of the first three doses of IPV. An additional IPV dose would be needed at age 4 to 6 years. There is no need to restart a series if the primary immunization schedule is interrupted; the next dose in the series should be given.[7] Prior doses of OPV, if documented, should be counted when considering whether there is a need for further polio immunization. Monovalent OPV doses of type 1 or 3 and bivalent doses of OPV containing only serotypes 1 and 3 should not be counted toward the US vaccination requirements because they do not induce immunity against polio serotype 2. OPV doses administered after April 1, 2016 are either bivalent OPV or monovalent OPV.[222]

The decision to move to an all-IPV schedule in the United States was based on the balance of benefit and risk. OPV rarely caused paralytic polio (with the greatest risk after the first dose [overall risk 1 per 670,000 first doses]), and IPV had eliminated disease without risk for serious side effects when given to a high proportion of people in developed countries, such as Sweden. In 1988, the World Health Assembly endorsed a goal to eradicate polio from the world. The major vaccine used in the worldwide eradication effort is OPV. Advantages of OPV include ease of use, superior induction of intestinal immunity to prevent wild poliovirus spread, spread of vaccine virus to unvaccinated contacts resulting in immunization of children not reached by vaccination programs, and lower cost than IPV. Extensive efforts in the Americas, including mass campaigns with OPV twice a year targeted to all children younger than 5 years regardless of prior immunization status, led to the elimination of polio in the Western Hemisphere. The last known case of polio caused by wild poliovirus in the Americas had its onset in Peru in 1991. The Western Hemisphere was certified free of polio in 1994,[46] and the European region of WHO was certified free of polio in 2002. Since 1988, almost all countries with endemic polio have conducted National Immunization Days, and in the setting of greatly improved surveillance, cases of polio caused by wild poliovirus have decreased from an estimated 350,000 in 1988 to 22 cases in 2017. By the end of 2017, only three countries—Nigeria, Pakistan, and Afghanistan—had never interrupted wild poliovirus transmission (www.polioeradication.org).[223]

In 2012 the Strategic Advisory Group of Experts (SAGE) on Immunization of WHO recommended that all countries implement at least one dose of IPV into their routine immunization schedules in preparation for moving from trivalent OPV to bivalent OPV (without type 2 virus). The switch from trivalent to bivalent OPV took place in 2016, and trivalent OPV is no longer available globally.[224] Eventually, all OPV use

will cease once eradication of wild polioviruses is certified (www.who.int/wer/2013/wer8801.pdf). (Also see Chapter 171.)

Polio vaccine is not recommended routinely for persons aged 18 years or older in the United States because the risk from wild virus is low, and most are immune as a result of vaccination during childhood. However, if vaccine is needed, such as for persons traveling to polio-endemic areas or to some countries bordering polio-endemic areas (see www.cdc.gov/travel for current list), or for certain categories of health care personnel who are at greater risk for exposure to polioviruses than the general population, previously unvaccinated adults should receive two doses of IPV at intervals of 4 to 8 weeks and a third dose 6 to 12 months after the second. Adults who have had a primary series of OPV or IPV and who are at increased risk for exposure to poliovirus may receive an additional one-time dose of IPV.

Adolescents may have received a four-dose series, with 4 weeks between each dose, and the final dose before the fourth birthday. This schedule is considered complete if the fourth dose was given on or after 18 weeks of age and was given before August 7, 2009 and if the adolescent is not traveling to a polio-endemic area. If an adolescent is traveling to a polio-endemic area and received a compressed schedule with a 4-week interval between doses, regardless of the timing of this schedule, he or she should receive an additional dose of IPV before travel.

Rabies Vaccine

Rabies vaccine is an inactivated virus vaccine prepared either in human diploid cell culture (HDCV) or in purified chick embryo cell culture (PCEC).[225] Rabies vaccination is recommended in two situations: as preexposure prophylaxis in persons likely to be exposed to rabies (e.g., veterinarians, forest rangers, travelers who may be at high risk based on countries and activities) and after exposure to animals known or suspected to be rabid. The primary preexposure immunizing course is three doses of rabies vaccine given intramuscularly at 0, 7, and 21 to 28 days. The three-dose course results in induction of protective levels of antibodies in virtually 100% of vaccinees. Serologic testing every 2 years is recommended to ensure that high-risk vaccinees maintain protective levels of antibody. Those whose titer falls to less than the recommended level should receive a booster. Alternatively, boosters may be administered every 2 years without serologic testing for persons at high risk for exposure. In the postexposure setting, four doses of rabies vaccine are given intramuscularly on days 0, 3, 7, and 14 to previously unimmunized persons. This deviates from the approved five-dose schedule in the package insert, so use of the four-dose schedule is off label. Persons who were previously fully vaccinated and who are exposed to rabies should receive IM doses of rabies vaccine on days 0 and 3. In all high-risk postexposure settings for previously unimmunized persons, rabies vaccine should always be used in conjunction with RIG (see "Rabies Immune Globulin"). Rabies vaccine should be administered by IM injection into the deltoid muscle in adults and children or the anterolateral thigh in infants; there have been reports of possible vaccine failure after gluteal administration.[226,227] Corticosteroids, other immunosuppressive agents, antimalarial drugs, and immunosuppressive illnesses can interfere with the immune response to rabies vaccine. There are no known contraindications to rabies vaccination in persons who are at risk or have been exposed (see Chapter 163).[225]

Rotavirus Vaccines

There are two licensed rotavirus vaccines in the United States: RotaTeq (RV5) (Merck) and Rotarix (RV1) (GlaxoSmithKline).[228] Both are oral live-attenuated virus vaccines. RV5 was developed through reassortment of a parent bovine rotavirus strain (WC3) with human strains, which donate either outer capsid proteins (G proteins) or attachment proteins (P proteins) to the WC3 strain. The resultant vaccine contains five separate viruses expressing human G1, G2, G3, G4, and P1A(8) proteins. The G proteins in the vaccine cover about 90% of the wild rotavirus strains detected in the United States from 1996 to 2005. Many of the other strains have the P1A(8) attachment protein. After a three-dose series, the efficacy against any G1 to G4 virus-associated gastroenteritis was 74%, and against severe gastroenteritis was 98%. RV5 reduced emergency department visits in an 11-country analysis by 94% and hospitalization by 96%. Of interest, the vaccine was effective against G9 wild-type rotaviruses. In the US schedule, doses of RV5 are recommended at 2, 4, and 6 months of age. The minimum age for the first dose is 6 weeks, and the maximum age is 14 weeks and 6 days. The minimum interval between doses is 4 weeks, and in the United States the maximum age for the last dose is 8 months, 0 days.

RV1 is an attenuated vaccine derived from a wild human rotavirus (G1P1A[8]).[229] In a large Latin American trial, the efficacy against severe rotavirus infection after two doses of vaccine was 85% up to age 1 year and 81% up to age 2 years. In a European trial, efficacy was higher: 87% against any rotavirus infection and 96% against severe disease. In self-controlled case series in Mexico and Brazil, the incidence rate ratio of intussusception was 2.6 to 5.3 in the first 7 days after a dose of rotavirus vaccine, compared with outside of the 7-day window.[229] Based on studies from the middle- and high-income countries of Mexico, Brazil, Australia, and the United States, it is believed that for every 20,000 to 100,000 rotavirus vaccinees, there will be one additional case of intussusception.[229,230,231,232] Important to note, in a self-controlled case series study from seven lower-income sub-Saharan African countries that introduced RV1, an increased risk of intussusception was not identified.[233] Rotavirus vaccine is contraindicated in infants with a history of intussusception. The rotavirus vaccination program has had major global success, with reductions in rotavirus hospital admissions of 73% and reductions in acute gastroenteritis deaths of 34% each year after the initiation of the vaccination program in Mexico and Brazil.[234] RV1 is recommended in a two-dose schedule, usually at 2 and 4 months of age. Minimum ages, minimum intervals, and maximum ages are the same as for RV5. In the United States there is no preference for one vaccine over another. Use of the same vaccine for all doses is recommended. When this is not feasible or when the type of vaccine used for prior doses is unknown, a total of three doses should be administered.

Preliminary data from population surveillance systems suggest that RV5 not only induces individual protection but may also provide community protection through herd protection.[228]

Rubella Vaccine

Rubella vaccine contains live-attenuated rubella virus grown in human diploid cells (RA27/3).[156] Other substrates, such as duck embryo cells or rabbit kidney cells, also have been used for rubella vaccines, but these vaccines are no longer available in the United States. When the vaccine is administered to a person on or after the first birthday, 95% or more of recipients can be expected to become immune. Immunity after a single dose is long lasting and appears likely to be lifelong. Boosters are not necessary, although many persons will receive a second dose as part of the two-dose MMR schedule to prevent measles and mumps. Rubella vaccine is recommended for all people on or after the first birthday, except those who have documentation of having received live rubella vaccine and those who have laboratory documentation of immunity to rubella. Most persons born before 1957 can be considered immune. It is particularly important to ensure that women of childbearing age are immune to rubella, because children born to mothers exposed to wild-type rubella in pregnancy can develop congenital rubella syndrome. Rubella vaccine virus is known to be able to cross the placenta and infect fetal tissue. Nonetheless, there were no instances of congenital rubella syndrome in the offspring of 226 susceptible women who received RA27/3 rubella vaccine within 3 months of conception and who carried their pregnancies to term.[235] In addition, thousands of pregnant women in Brazil received rubella vaccine during pregnancy, and there were no identified cases of congenital rubella syndrome as a result. This indicates that the risk for congenital rubella syndrome from vaccine virus, if there is any risk, is very low. Notwithstanding the fact that no observable risk has been associated with rubella vaccine administered during pregnancy, rubella vaccine should not knowingly be administered to a pregnant woman. A reasonable approach is to ask women whether they are pregnant or may become pregnant within the next month, exclude those who answer affirmatively, and vaccinate the others, after explaining the theoretical risk to them.[156]

Known adverse events associated with rubella vaccine include low-grade fever and rash in 5% to 10% of recipients and joint pain with or without objective manifestations of arthritis. The latter occurs with

increasing frequency in older individuals; about 25% of susceptible women may have transient arthralgia after rubella vaccination.[236,237] Acute arthritis is seen in about 10% of susceptible women. The risk for arthritis after rubella vaccine is substantially lower than the risk after natural rubella. The IOM reviewed the adverse consequences of rubella vaccination and favored acceptance that the vaccine was a cause of transient arthralgia in women and children.[119] However, there is no evidence of increased risk for new onset of chronic arthropathies among women vaccinated with RA27/3 vaccine.[238–240] With regard to other illnesses temporally related to rubella vaccine, the IOM concluded that the evidence was insufficient to implicate rubella vaccine as a cause of thrombocytopenic purpura, radiculoneuritis, and other neuropathies. Thrombocytopenic purpura had been associated with MMR vaccine, but the 1994 IOM report does not discuss thrombocytopenic purpura in association with this vaccine.[65]

Previous experience with programs involving serologic screening and subsequent vaccination of susceptible individuals has demonstrated a low success rate in delivering vaccinations to identified susceptible persons (typically approximately 30%–50%). Contraindications to rubella vaccination are pregnancy and an immunocompromised state (see "Measles-Containing Vaccine").[147] Despite the success of the rubella immunization program in the United States, cases of congenital rubella syndrome continue to occur from viruses either acquired from other countries or imported into the United States.[157]

Smallpox Vaccine

Effective use of smallpox vaccine eradicated smallpox as a naturally occurring disease in 1977.[241] The vaccine is a live-unattenuated preparation of vaccinia virus that induces protection against smallpox virus in 95% or more of recipients. ACAM2000 (Acambis, Cambridge, MA), produced in Vero cells, is the current licensed preparation of smallpox vaccine.[242]

Routine use of smallpox vaccine among the civilian population in the United States was discontinued in 1972 and by the military in 1990. In May 1983, Wyeth Laboratories, the only active licensed producer in the United States, discontinued general distribution of smallpox vaccine, making it no longer available. Acambis manufactures ACAM2000, which was licensed in 2007 and is the only licensed available smallpox vaccine in the United States. Smallpox vaccine was recommended in 2003 for members of public health and health care response teams[243] and for selected military personnel; it continues to be available as an investigational new drug for individuals working with vaccinia or other orthopoxviruses. Smallpox vaccine is administered intradermally by means of the multiple puncture technique with a presterilized bifurcated needle. With the bifurcated needle held perpendicular to the skin, punctures are made rapidly, with sufficient pressure that a trace of blood appears after 15 to 20 seconds.

Previously recognized adverse events associated with smallpox vaccine include disseminated vaccinia, eczema vaccinatum, vaccinia necrosum (progressive vaccinia), and encephalitis.[244–246] The risk for transmission of vaccinia virus from the inoculation site can be reduced by keeping the vaccine site covered with gauze and a layer of clothing and by good hand hygiene. For persons involved in patient care, addition of a semipermeable dressing is recommended.[245] In the 2003 public health and military vaccination program, smallpox vaccine was contraindicated for persons younger than 1 year; persons with a history or presence of eczema, atopic dermatitis, or other dermatologic conditions that are exfoliative; persons with conditions associated with immunosuppression; persons who were pregnant or are breastfeeding; or persons with a serious allergy to any component of the vaccine. After reports of ischemic cardiac events in recent vaccinees, persons with known underlying heart disease or three or more known major cardiac risk factors were also excluded from the preevent vaccination program,[246] although no causal relationship has been established between receipt of the vaccine and ischemic cardiac disease.

Inflammatory cardiac disease (myocarditis, pericarditis, or myopericarditis) was recognized in 2003 among recipients of smallpox vaccine in both military and civilian programs.[247] Although myocarditis had been previously reported in Europe and Australia after administration of other vaccinia strains, it was not previously recognized as an adverse event after use of the New York City Board of Health (NYCBOH) strain, the strain used for production of Wyeth's smallpox vaccine in the United States. The clinical spectrum of illness ranges from mild symptoms to heart failure, and the natural history remains unknown; it is unclear if all patients recover completely, or if some persons with subclinical myocarditis may later develop dilated cardiomyopathy, as is thought to occur with some patients who have other types of myocarditis. Histopathologic data are limited, but in one patient who underwent endomyocardial biopsy, an eosinophilic infiltrate without presence of vaccinia virus was found. Onset is typically 7 to 19 days after vaccination; the frequency appears to be approximately 1 in 10,000 vaccinees.[247]

Other vaccinia strains, such as modified vaccinia Ankara, which undergoes only limited replication in humans, are under active study as vaccine strains that might be associated with a lower incidence of adverse events or might be safe to use in populations in which current smallpox vaccines are contraindicated (e.g., immunocompromised persons).[241]

Tetanus Toxoid

Tetanus toxoid, a purified preparation of inactivated tetanus toxin, is one of the most effective immunizing agents known. Tetanus toxoid is recommended for use in all residents of the United States for whom contraindications do not exist.[92] Tetanus toxoid should always be used in combination either with diphtheria toxoid alone or with diphtheria toxoid and pertussis vaccine to ensure protection against both diseases. Five doses of DTaP are given at 2, 4, 6, and 15 to 18 months, and at 4 to 6 years of age. A primary course of two doses administered 4 to 8 weeks apart, with a third dose given 6 to 12 months later, induces protective antibodies in more than 95% of recipients and is recommended for all unvaccinated older children and adults. After childhood DTP/DTaP immunization, booster doses with adult formulation tetanus and diphtheria toxoids (Td) are recommended at age 11 to 12 years and then every 10 years thereafter. A one-time dose of Tdap may be substituted for one of the recommended Td boosters. For unvaccinated children in the first year of life for whom pertussis vaccine is contraindicated, pediatric DT should be substituted for DTaP. For unvaccinated children in the second year of life for whom pertussis vaccine is contraindicated, two doses of DT should be administered 4 to 8 weeks apart, with a third dose 6 to 12 months later (see "Pertussis-Containing Vaccine"). DTaP or DT is given to children younger than 7 years. Common adverse effects include local reactions and fever. In some persons who have received multiple doses of tetanus toxoid, Arthus-like reactions have been described.[248] Tetanus toxoid has been suggested as a rare cause of brachial plexus neuropathy. The IOM concluded that tetanus toxoid causes brachial neuritis in the first month after immunization at a rate of 0.5 to 1 case per 100,000 toxoid recipients.[65] Tetanus toxoid also has been implicated as a cause of GBS. The most convincing evidence comes from a case report of one individual who acquired GBS three times with successive administrations of tetanus toxoid.[249] However, population-based studies in both children and adults have revealed an incidence of GBS within expected limits and do not support a causal role.[250] If tetanus toxoid causes GBS, it does so rarely.[251] The only contraindication is in individuals who previously had neurologic or severe hypersensitivity reactions after tetanus toxoid. Table 316.5 summarizes the ACIP-recommended approach to use of tetanus toxoid and tetanus IG for PEP of tetanus.

Typhoid Vaccine

Two preparations of typhoid vaccine are available in the United States: an oral live-attenuated strain of *Salmonella* Typhi (Ty21a) and a Vi capsular polysaccharide vaccine (ViCPS). The two vaccines provide between 33% and 80% protection after a primary series.[252,253] The CDC recommends typhoid vaccine for travelers to areas where there is an increased risk of exposure to *Salmonella enterica* serotype Typhi. Typhoid vaccines are indicated for travelers who will have prolonged exposure to contaminated food and drinks in developing countries, those with prolonged exposure to typhoid carriers, and laboratory personnel who work with *Salmonella* Typhi.

The oral vaccine comes as an enteric-coated capsule that should be taken on alternate days with cool liquid approximately 1 hour before

TABLE 316.5 Summary Guide to Tetanus Prophylaxis in Routine Wound Management: United States

HISTORY OF ADSORBED TETANUS TOXOID (DOSES)	CLEAN, MINOR WOUNDS		ALL OTHER WOUNDS[b]	
	Td or Tdap[c]	TIG	Td or Tdap[c]	TIG
Unknown or <3	Yes	No	Yes	Yes
3[d]	No[e]	No	No[f]	No

[a]Important details are in the text.
[b]Such as, but not limited to, wounds contaminated with dirt, feces, soil, saliva, and so on; puncture wounds; avulsions; and wounds resulting from missiles, crushing, burns, and frostbite.
[c]For children younger than 7 years, DTaP or DTP (DT if pertussis vaccine is contraindicated) is preferred to tetanus toxoid alone. For persons 7 years and older, Td is preferred to tetanus toxoid alone, unless Tdap is indicated.
[d]If only three doses of fluid toxoid have been received, a fourth dose of toxoid, preferably an absorbed toxoid, should be given.
[e]Yes, if more than 10 years since last dose.
[f]Yes, if more than 5 years since last dose. (More frequent boosters are not needed and can accentuate side effects.)
DT, Diphtheria and tetanus toxoids (pediatric) vaccine; *DTaP;* diphtheria and tetanus toxoids and acellular pertussis (pediatric) vaccine; *DTP,* diphtheria, tetanus, and pertussis; *Td,* tetanus and diphtheria toxoids (adult) vaccine; *Tdap,* tetanus, diphtheria, and acellular pertussis (adult) vaccine; *TIG,* tetanus immune globulin.

a meal. The four recommended doses should be refrigerated until needed. Data are not available to make recommendations about the need for boosters with the oral vaccine, although the manufacturer recommends a new complete series every 5 years. The ViCPS is recommended as a single 0.5-mL dose. Boosters are recommended every 2 years. The Ty21a vaccine is not recommended for children younger than 6 years. The ViCPS is recommended for persons 2 years or older. Evidence from trials and postmarketing studies suggests that parenteral Vi vaccines are usually tolerated well. In a manufacturer-funded postmarketing safety study conducted in 11 US travel clinics, the most common reactions were injection site pain (77%), tenderness (75%), and muscle aches (39%).[254] The Ty21a and the ViCPS vaccines cause fever and headache in less than 6% of recipients. Other adverse reactions to the oral preparation are rare and consist of abdominal discomfort, nausea, and vomiting. Local reactions to the ViCPS have been reported in 7% of recipients. The oral vaccine should not be given to persons who are immunocompromised, including those with HIV infection. Ty21a should not be given to a person taking antibiotics unless at least 72 hours have elapsed since the last dose.

Varicella Vaccine

Two varicella vaccine products are available in the United States: a single-component product (Varivax; Merck) and a combined vaccine with MMR (MMRV, ProQuad; Merck).Both use the Oka/Merck strain of varicella-zoster virus (VZV). The VZV titer in MMRV (minimum of 3.99 $\log_{10}$ plaque-forming units [PFU] per dose) is higher than in the single-component vaccine, which is about 3.13 $\log_{10}$ PFU per dose. Live-attenuated varicella vaccine was licensed in the United States in 1995. MMRV was licensed in 2005. One dose of vaccine generally had been found to be highly effective against severe varicella (95%–100%) and moderately effective against mild disease (70%–90% in most studies).[255–261] Most vaccinees who acquire varicella (breakthrough disease) tend to have mild illness with fewer than 50 lesions, compared with 250 to 500 lesions in unvaccinated persons with disease. Immunity appears to be long lasting. However, the rate of breakthrough disease in the 10 years after a single dose was 7.3% in one study.[262] In contrast, only 2.2% of children who received two doses had varicella. Most of the breakthrough episodes occurred in the first 5 years. Given the benefits of two doses in reducing vaccine failure, a two-dose schedule is now recommended.[57] The vaccine is recommended routinely for all children at 12 to 15 months of age, with a second dose to be given at 4 to 6 years of age as varicella vaccine or MMRV. The second dose may be administered earlier than age 4 to 6 years, with the minimum interval being 3 months. HIV-infected children who are asymptomatic and not immunosuppressed should receive two doses of varicella vaccine, with the first dose at age 12 to 15 months or older and with a 3-month interval between doses.[57,263] However, only single-component varicella vaccine should be used in HIV-infected children; MMRV should not be used because of a theoretical risk of uninhibited replication of a high-titer vaccine virus causing an adverse reaction.

MMRV is associated with a higher risk for fever than simultaneous administration of MMR and varicella at different sites, and also causes an increased risk for febrile seizures after dose one of the two-dose series.[159] In June 2009, after consideration of the postlicensure data and other evidence, ACIP adopted new recommendations regarding the use of MMRV vaccine for the first and second doses and identified a personal or family (i.e., sibling or parent) history of seizure as a precaution for use of MMRV vaccine. For the first dose of measles, mumps, rubella, and varicella vaccines at age 12 to 47 months, either MMR vaccine and varicella vaccine or MMRV vaccine may be used. Providers who are considering administering MMRV vaccine should discuss the benefits and risks of both vaccination options with the parents or caregivers. Unless the parent or caregiver expresses a preference for MMRV vaccine, the CDC recommends that MMR vaccine and varicella vaccine should be administered simultaneously but at separate sites for the first dose in this age group. For the second dose of measles, mumps, rubella, and varicella vaccines at any age (15 months to 12 years) and for the first dose at age 48 months or older, use of MMRV vaccine generally is preferred over separate injections of its equivalent component vaccines (i.e., MMR vaccine and varicella vaccine). For persons aged 48 months or older, MMRV is usually preferred for the first dose if vaccination against varicella is also needed. MMRV is not associated with an increased risk of febrile seizures when it is the second dose of an MMR-containing vaccine.[160,265]

Vaccination has also been demonstrated to be effective for outbreak control in persons of all ages.[266,267] Vaccine also can be given routinely to any susceptible older child or adult, except persons with certain immunocompromising conditions. Persons aged 13 years and older should receive two doses 4 to 8 weeks apart. Adults who might be at increased risk for exposure or transmission and who do not have evidence of immunity should receive special consideration for vaccination; such persons include (1) health care providers, (2) household contacts of immunocompromised persons, (3) persons who live or work in environments in which transmission of VZV is likely (e.g., teachers, daycare employees, residents and staff in institutional settings), (4) persons who live or work in environments in which transmission has been reported (e.g., college students, inmates and staff members of correctional institutions, and military personnel), (5) nonpregnant women of childbearing age, (6) adolescents and adults living in households with children, and (7) international travelers. Because adults are at higher risk for complications from varicella than are children, vaccination of all susceptible adolescents and adults is desirable. Persons with the following are considered to have evidence of immunity: (1) a diagnosis or verification of a history of varicella disease or zoster by a health care provider; (2) laboratory evidence of immunity; (3) documentation of age-appropriate vaccination (one dose for children aged 12 months through 3 years and two doses for persons aged 4 years old and older); or (4) birth in the United States before 1980 (excluding health care providers, pregnant women, and immunocompromised persons). Although a negative or uncertain history of varicella in young children is predictive of

susceptibility, most young adults with such histories are immune. In some settings, serologic screening of persons with negative or unknown prior histories of varicella is cost-effective.[268] However, recalling and vaccinating identified susceptible persons may be difficult, making vaccination with use of history as the determinant of need more attractive.

The most common adverse events are local reactions and rash. In children, about 3% acquire a varicella-like rash at the injection site, with a median of two lesions. Local reactions are more common after the second dose (25% in children and 33% in adults) versus the first dose (22% in children and 24% in adults). Four percent of children acquire a generalized rash, with a median of five lesions. In adults, 3% and 1% acquire localized rashes after the first and second doses, respectively, whereas 6% and 1% acquire more generalized rashes after the first and second doses, respectively.[57] Transmission of vaccine virus has been reported rarely and only from persons with rash. There is no evidence that vaccination increases the risk for zoster. In fact, in vaccinated children, zoster incidence after vaccination is lower than would be expected after natural infection.[269,270] Vaccine is contraindicated in persons with anaphylactic hypersensitivity to vaccine components, including neomycin and gelatin, and in most persons with deficiencies of cell-mediated immunity.[57] Available data on the safety and efficacy of varicella vaccine in HIV-infected children who were not severely immunocompromised suggests that varicella vaccine is immunogenic and that the vaccine safety profile is acceptable.[271,272] Persons who are immunocompromised or receiving immunosuppressive drugs should not receive varicella vaccine from a period 2 weeks before to 3 months after immunosuppressive therapy, and they should be deemed immunocompetent when they receive the vaccine. Pregnant women should not be vaccinated, and women should be advised not to become pregnant for 1 month after vaccination.[57]

Varicella vaccine is more thermolabile than other vaccines. It must be stored frozen at an average temperature of −50°C to −15°C.

Yellow Fever Vaccine

Yellow fever vaccine is a live-attenuated virus preparation that is highly effective in inducing protection in recipients.[273] This vaccine is indicated for use in travelers going to yellow fever–endemic areas and may be required for entry into some countries (see wwwnc.cdc.gov/travel/diseases/yellow-fever). Only a single dose of subcutaneously administered vaccine is required. A booster dose after a 10-year interval is recommended for those who received a first dose while HIV infected or while pregnant. Otherwise, boosters are not generally recommended, but depending on the destination, they may be required every 10 years, although the vast majority of persons retain immunity well past 10 years. Children younger than 6 months appear to be at highest risk for severe neurotropic reactions, and vaccine is contraindicated in this age group. Other contraindications include anaphylactic hypersensitivity to eggs and immunocompromised states. If possible, vaccination of infants should be delayed until 9 months of age. Pregnancy is not considered an absolute contraindication; however, it is recommended that administration of the vaccine be postponed until after completion of pregnancy, if possible. Other precautions include children 6 to 8 months of age, persons with asymptomatic HIV infection with T-lymphocyte counts less than 500/mm^3, and women who are breastfeeding. Adverse reactions (fever, aches and soreness, redness or swelling where the injection was given) occur in up to 25% of vaccinees. Anaphylaxis has been reported in 0.8 to 1.8 persons per 100,000 doses of vaccine distributed. A rare syndrome (0.25 cases per 100,000 doses distributed) after yellow fever vaccination—febrile multiorgan system failure or viscerotropic disease—has been reported, with high rates of mortality, primarily among older adults and persons who have undergone thymectomy or have severe thymic dysfunction being vaccinated for the first time. Neurotropic disease has also been reported after yellow fever vaccination in 1 to 2 persons per 100,000 doses distributed and is also more common in older vaccinees. It manifests as several distinct clinical syndromes, including meningoencephalitis (neurotropic disease), GBS, acute disseminated encephalomyelitis, and bulbar palsy. Yellow fever vaccine should be administered with caution and only after careful counseling in patients older than 60 years who are going to spend time in yellow fever–endemic zones. Yellow fever vaccine should not be given to immunocompromised persons or persons with anaphylactic allergies to eggs, chicken protein, or gelatin.

Because of a shortage of YF-VAX, Sanofi Pasteur has imported Stamaril, a yellow fever vaccine distributed in France. Stamaril has a similar safety profile to YF-VAX, but because it is distributed under an Emergency Use Authorization (EUA), there are some differences in contraindications and precautions. For Stamaril, HIV infection with no evidence of immunosuppression is a precaution; breastfeeding for the first 14 days after vaccination is an exclusionary criterion and therefore effectively a contraindication; and age 6 to 8 months is an exclusionary criterion and therefore effectively a contraindication.

Zoster Vaccine

Zoster vaccine is designed to boost immunity to VZV in persons previously infected with the virus, to either prevent shingles by inhibiting the reactivation of virus from dorsal nerve ganglia or to lower the severity and health burden of shingles, should it occur.[274]

An adjuvanted subunit vaccine, RZV, is licensed and has superior efficacy to live-attenuated zoster vaccine (ZVL) with no serious adverse events associated with vaccination. Efficacy of RZV over 3 years for prevention of zoster is 97% in 50- to 59-year-olds, 97% in 60- to 69-year-olds, and 91% in persons aged 70 years or older. Safety trials detected injection site reactions, myalgias, fatigue, headache, shivering, fever, and gastrointestinal illness. These were severe enough to cause interference in daily activity in one in six recipients. Two doses of vaccine are recommended for immunocompetent persons aged 50 years or older; the second dose is recommended 2 through 6 months after the first dose. ACIP preferentially recommends the use of this two-dose vaccine over the live zoster vaccine (ZVL). ZVL is a lyophilized preparation of the Oka/Merck strain and differs from varicella vaccine in potency. In a trial of vaccine in adults aged 60 years or older and with a history of prior varicella, a single dose of vaccine was 51% effective in decreasing the incidence of zoster, 61% effective in reducing the overall burden of illness from shingles, and 67% effective in reducing the incidence of postherpetic neuralgia (PHN) in the vaccinated cohort. Of persons who actually developed zoster, PHN was reduced by 39% in vaccinees compared with placebo recipients who had shingles. Effectiveness in preventing zoster tended to decrease with increasing age, with the highest efficacy among 60- to 69-year-olds. For persons aged 80 years and older, the point estimate for vaccine effectiveness was positive, but the 95% CI overlapped zero, indicating that the estimate was not statistically significant.[275] A follow-up study demonstrated 70% efficacy in prevention of zoster in 50- to 59-years-olds, and the FDA lowered the age of approval to 50 years. RZV is recommended regardless of a past history of zoster disease and regardless of past use of ZVL.

No particular clinical pattern was noted to implicate vaccine in causing specific adverse events. Zoster vaccine is indicated for the routine vaccination of persons aged 60 years and older without contraindications. Although the FDA licensed the vaccine for persons aged 50 years or older, ZVL is currently recommended only for persons aged 60 years or older because zoster disease incidence continues to rise as one ages, and the vaccine protection wanes over time, with less than 40% protection 5 years after receipt of ZVL. Persons with a prior history of zoster can be vaccinated. ZVL is contraindicated in persons with allergy to vaccine components and moderate or severe immunodeficiency.

Immunoglobulin Preparations

Passive immunization can be provided by preformed antibodies in several types of products used to treat persons with primary and, less frequently, secondary immune deficiency and to prevent or, less frequently, to treat certain infectious diseases. The choice is made in part according to the types of products available, the type of antibody desired, the route of administration, and the conditions or diseases being treated. Products used include (1) IG administered through the IM route, (2) specific or hyperimmune IG preparations administered through the IM route, (3) IGIV; (4) specific (hyperimmune) IG administered through the IV route, (5) antibodies of animal origin, (6) monoclonal antibodies, and (7) IG subcutaneous (human) that has been approved for treatment

of patients with primary immune deficiency states (see Table 316.4). Indications for administration of IG preparations other than those relevant to infectious diseases are not included in this chapter.

Intramuscular Immune Globulin

IM IG is prepared from pooled human adult plasma by means of an alcohol-fractionation procedure. IG consists primarily of IgG and trace amounts of IgA and IgM, is sterile, and is not known to transmit any infectious agents, including hepatotropic viruses and HIV. IG is a concentrated protein solution containing specific antibodies reflective of the infectious disease exposure and immunization experience of persons from whom the plasma was obtained to prepare the IG. More than 1000 and up to 60,000 donors per lot are used to include IG from persons with a broad spectrum of antibodies. Individual donors are screened for markers of a variety of viruses to minimize potential transmission of infection. IG is licensed and recommended for administration deep into a large muscle mass, such as the gluteal region, or into the anterior thigh of a child. IV use of human IG is contraindicated.

Indications for Use of Intramuscular Immune Globulin

The three indications for use of IG are replacement therapy for antibody deficiency disorders, and prophylaxis against hepatitis A and measles viruses.[40,105,156,276]

Replacement therapy for antibody deficiency disorders. For most patients, IM IG has been replaced by IGIV or subcutaneously administered IG because use of IGIV results in higher total plasma IG concentrations, and higher titers of specific antibodies can be achieved with minimal discomfort.

Hepatitis A prophylaxis. In persons 12 months and older, hepatitis A immunization is preferred over IG for PEP against hepatitis A virus infections. In persons 6 months and older, hepatitis A immunization is preferred over IG for persons traveling to areas where hepatitis A is endemic.[274] For immunocompromised persons indicated for vaccination, both vaccine and IG should be administered. For persons younger than 12 months, IG is preferred to hepatitis A immunization. IG is effective in preventing hepatitis A when administered within 14 days of exposure (dose of 0.1–0.2 mL/kg) or when given before exposure in somewhat larger quantities (dose of 0.1 mL/kg for trips less than 1 month or 0.2 mL/kg for trips of 1 month or longer).

Measles prophylaxis. Immunization against measles is the optimal method for achieving protection against measles. IG administered to exposed, measles-susceptible persons can prevent or modify measles if administered within 6 days of exposure (IG IM dose of 0.5 mL/kg, up to a maximum of 15 mL, IGIV dose of 400 mg/kg IV).[40,156]

Specific Intramuscular Immune Globulin Preparations

The term *hyperimmune globulin* is used to refer to a group of products known as specific IGs. These products differ from other preparations in selection of donors who have been immunized or given booster immunizations and often in the number of donors from whom plasma is included in the product pool. Donors known to have high titers of the desired antibody are selected. Specific IG preparations are prepared by the same procedure as used for other IG preparations. Products in this category include HBIG, RIG, TIG, and VariZIG.

Hepatitis B immune globulin. HBIG is prepared from plasma preselected for high titer of antibody to HBsAg. In the United States, HBIG has an anti-HBsAg titer of more than 1 : 100,000 by radioimmunoassay.[109,114] HBIG is recommended for use in postexposure settings for susceptible individuals who have been exposed to known HBV, to infected sexual partners, or to blood containing HBsAg by the percutaneous or mucous membrane route. The dose is 0.06 mL/kg given immediately for both sexual contacts and persons exposed percutaneously. The hepatitis B vaccine series should be started simultaneously in those who previously have not been vaccinated. Alternatively, a second dose of HBIG may be given 1 month later in persons for whom hepatitis B vaccine is not indicated. All pregnant women should be tested for circulating HBsAg. HBIG is recommended for infants born to HBsAg-positive women. A dose of 0.5 mL should be given as soon as possible after birth, but within 12 hours of delivery in conjunction with a dose of hepatitis B vaccine. Additional doses of vaccine are indicated at 1 month and 6 months of age. The only known adverse effect is local discomfort at the site of injection. There are no known precautions or contraindications.[112]

Rabies immune globulin. RIG is a hyperimmune globulin derived from humans who have been immunized against rabies and have very high titers of antibodies to rabies.[225] RIG is designed for management of persons who have been exposed to rabid animals. RIG always should be used in conjunction with rabies vaccine in previously unvaccinated persons. However, if more than 8 days have elapsed since the first dose of rabies vaccine, RIG is unnecessary because an active antibody response to the vaccine presumably has begun. Experience indicates that administration of a full course of HDCV or PCEC vaccine with RIG is 100% effective in preventing development of rabies after exposure to known rabid animals. As much as possible of the 20 IU/kg dose should be infiltrated into and around the wound. Any remaining RIG should be administered intramuscularly at a different site from vaccine. Adverse effects include minor local discomfort. There are no known contraindications.[225]

Tetanus immune globulin. TIG is a hyperimmune globulin indicated for management of tetanus-prone wounds in persons who have no prior history of tetanus immunization.[92,93,197] The standard dose is 250 units intramuscularly. Local reactions are rare, and there are no known contraindications. If used, TIG should be administered simultaneously with, but at a different site from, combined tetanus-diphtheria toxoids (Td) or combined tetanus-diphtheria-acellular pertussis (Tdap) vaccine if pertussis vaccine is also indicated. Primary immunization against tetanus and diphtheria should then be completed using the routine schedule. Table 316.5 summarizes the ACIP-recommended approach to PEP of tetanus.[92] For the treatment of tetanus, TIG in large doses (3000–6000 units) also is recommended, with wound cleaning and débridement, antibiotics, and supportive care.

Varicella-zoster immune globulin. VariZIG is a purified human IG preparation made from plasma containing high titers of VZV antibodies.[57] The decision to administer VariZIG depends on these factors: (1) the likelihood that the exposed person has no evidence of immunity to varicella, (2) the probability that a given exposure to varicella or zoster will result in infection, and (3) the likelihood that the patient is at greater risk than the general population for developing complications of varicella if infected. Furthermore, the criteria for use are limited to immunocompromised persons, pregnant women, neonates whose mothers have varicella rash 5 days before to 2 days after delivery, hospitalized preterm infants born at 28 weeks of gestation or later whose mothers do not have evidence of immunity to varicella, and hospitalized preterm infants born at less than 28 weeks' gestation, regardless of the immune status of the mother.[277] If these criteria are met, and if the exposure occurred less than 10 days previously, VariZIG should be administered. VariZIG is commercially available from a broad network of specialty distributors in the United States (list available at www.varizig.com).

VariZIG is given intramuscularly at the recommended dose of 125 units/10 kg of body weight up to 625 units (i.e., five vials). The product may not prevent infection; however, if infection occurs, it is usually subclinical or mild. Any person to whom VariZIG is administered to prevent varicella subsequently should receive age-appropriate varicella vaccine, provided the vaccine is not contraindicated. Varicella vaccine should be delayed until 5 months after VariZIG administration to ensure optimal response. Varicella vaccine is not needed if the patient develops varicella after VariZIG administration. Local reactions are rare. Contraindications for VariZIG include a history of anaphylactic or severe systemic reactions to human IGs and IgA-deficiency with antibodies against IgA and a history of hypersenstivitiy.[277]

Immune Globulin Intravenous

IGIV is made from pooled plasma of adults by using methods designed to prepare a product for IV use. The number of donors ranges from 15,000 to 60,000. IGIV consists of greater than 95% IgG and trace amounts of IgA and IgM. The FDA specifies that all IGIV preparations must have a minimum concentration of antibodies to measles virus, *Corynebacterium diphtheriae,* poliovirus, and HBV. Antibody concentrations against other

pathogens vary widely among products. Not all IGIV products have been approved or studied for all FDA-approved indications.

Indications for Use of Immune Globulin Intravenous

IGIV initially was formulated for IV use in patients with primary immunodeficiencies, enabling them to receive enough IG at regular intervals for protection against certain infections. Administration of IGIV results in an immediate rise in both total IgG and titers of specific antibodies. IGIV is approved by the FDA for seven conditions: (1) primary immunodeficiency status, (2) Kawasaki disease, (3) immune-mediated thrombocytopenia, (4) pediatric HIV infection, (5) secondary immunodeficiency in chronic lymphocytic leukemia, (6) prevention of graft-versus-host disease and infection in adults with HSCT, and (7) PEP for measles exposure for immunosuppressed individuals. IGIV products also are used for many other conditions, although demonstrated efficacy from controlled trials is not available in all cases.

Specific Immune Globulins for Intravenous Use

There are three specific plasma-derived IG products for IV administration for prophylaxis or therapy of infectious diseases: cytomegalovirus (CMV) IGIV, botulism IGIV (for infant botulism), and vaccinia IG. An IM humanized mouse monoclonal antibody preparation used to prevent respiratory syncytial virus (RSV) is available (see "Respiratory Syncytial Virus Immune Globulin and Palivizumab").

CMV IGIV has been developed and is indicated for prophylaxis of disease in seronegative organ transplant recipients. Use of CMV IGIV for prophylaxis of CMV disease varies among transplantation centers. Risk factors for development of CMV among transplant recipients include type of organ, immunosuppressive therapy, and the donor-recipient CMV status. CMV-negative transplant recipients who receive an organ from a CMV-positive donor are at the highest risk for CMV disease and generally receive some form of CMV prophylaxis.

Botulism IGIV for human use (BabyBIG) is a human-derived antitoxin licensed by the FDA for treatment of infant botulism caused by *Clostridium botulinum* type A or type B. BabyBIG is made and distributed by the California Department of Public Health (24-hour telephone number: 510-231-7600; www.infantbotulism.org). BabyBIG has been shown to decrease significantly the number of days on mechanical ventilation, days of intensive care unit stays, and overall hospital stay.[278] An equine-derived antitoxin is available for use in adults with botulism but is *not* used in infants.

Vaccinia Immune Globulin

Vaccinia immune globulin (VIG), an IM preparation, is a hyperimmune globulin prepared for treatment of certain complications of vaccinia vaccination. VIG is indicated for treatment of severe cases of inadvertent inoculation with smallpox vaccine, eczema vaccinatum, severe generalized vaccinia, and progressive vaccinia. VIG use should be considered in patients with severe ocular complications other than isolated keratitis. VIG is not recommended for treatment of postvaccinial encephalitis or encephalomyelitis, myopericarditis after smallpox vaccination, mild cases of generalized vaccinia, erythema multiforme, or isolated vaccinia keratitis. A preparation of VIG suitable for IV use (VIG-IGIV) is manufactured by Calgene, Canada; has been approved by the FDA; and is available through the CDC (under Investigational New Drug [IND] protocols) and the US Department of Defense.[246]

Respiratory Syncytial Virus Immune Globulin and Palivizumab

IG against RSV is licensed in the United States for administration to infants and children at high risk of severe disease caused by RSV; groups at high risk include infants and children younger than 24 months with chronic lung disease or a history of preterm birth (35 weeks gestational age or younger). RSV-IGIV, a hyperimmune globulin formulated for IV administration, is no longer produced in the United States.[279] Palivizumab is a humanized monoclonal antibody against the F protein of RSV and is produced by recombinant DNA technology. The recommended dosage is 15 mg/kg administered intramuscularly monthly throughout the RSV season. Palivizumab has been demonstrated to be effective in reducing the risk for RSV hospitalization.[280] No significant adverse events have been associated with palivizumab, and there is no interference with the immune response to live virus vaccines. The AAP has recommended that because of the high cost of these interventions, their use be limited to those infants and children at highest risk for severe RSV disease. The AAP recommendations for use in premature infants are based on risk (chronic lung disease, preterm birth, chronic heart disease, neuromuscular disorders [consider not a full recommendation], and immunodeficiencies [consider not a full recommendation]), the time of year (start of the RSV season [which is based on location]), and age during the location-based RSV season.[281–284]

Adverse Reactions to Immune Globulin Preparations

The most common adverse effects of intramuscularly administered IG include local pain at the injection site and, less commonly, flushing, headache, chills, and nausea. Serious systemic events are rare. Anaphylactic reactions have been reported after repeated administration to IgA-deficient persons.[285] Other than prior anaphylactic reactions, there are no known contraindications to use of the product. IG inhibits response to certain live-virus vaccines (e.g., measles and rubella vaccines) for a period of 3 to 11 months, depending on the dose administered.[286]

Severe reactions to IGIV occur infrequently, but mild adverse events have been associated with up to 20% of infusions. The "Adverse Reactions" sections of package inserts of specific products provide details.

Simultaneous administration of IG with hepatitis A vaccine may result in a decrease of the ultimate titer of hepatitis A antibody achieved but does not influence seroconversion and presumed protection.[105]

Hepatitis C has been transmitted by IGIV in both Europe and the United States and by an IV Rh IG preparation in Ireland.[287–289] Hepatitis C virus RNA has been detected with polymerase chain reaction in various IG preparations,[290] but the significance of this finding is unclear; disease has not been associated with products other than those noted previously. In response to these findings, manufacturing procedures have been modified to add new viral inactivation steps.[291]

Immune Globulin Subcutaneous

Subcutaneous administration of IG using battery-driven pumps has been shown to be safe and effective in adults and children with primary immunodeficiencies. Smaller doses administered more frequently (i.e., weekly) result in more even serum IgG concentrations over time. Systemic reactions are less frequent than with IV therapy, and some parents or patients can be taught to infuse the product at home. The most common adverse effects of subcutaneous administration of IG are injection-site reactions, including local swelling, redness, itching, soreness, induration, and local heat. There is only one product licensed in the United States for subcutaneous use. There are no data on administration of IgG via the subcutaneous route for conditions requiring high-dose IG therapy.

Rh Immune Globulin

Rh IG is a hyperimmune globulin prepared for use in Rh-negative women who have just delivered Rh-positive infants or have had a miscarriage or abortion of an Rh-positive fetus. When administered within 24 hours of the time of delivery or abortion, it is highly effective in preventing sensitization of the mother to Rh-positive red blood cells that might be present in a future pregnancy. Appropriate administration of Rh IG has reduced the occurrence of Rh hemolytic disease of the newborn in the United States to very low levels. Further reductions will require more careful attention to the administration of the product after abortion or delivery in all women for whom it is indicated. There are essentially no adverse effects associated with the product, and there are no known contraindications.[159]

USE OF VACCINES

Routine

Children

The 2018 recommended schedule for administration of vaccines to infants, children, and adolescents is shown in Fig. 316.1A.[73] Catch-up schedules for children 4 months to 6 years of age and 7 to 18 years of age and adolescents are shown in Fig. 316.1B and are available at

www.cdc.gov/vaccines/schedules/hcp/imz/catchup.html. The schedules are updated annually and are available at www.cdc.gov/vaccines/schedules/index.html.

It is recommended that all children and adolescents receive all vaccines listed in the table unless medical contraindications exist.[73] Five doses of DTaP and four doses of polio-containing vaccines are recommended. The fifth dose of DTaP and the fourth dose of polio vaccine are recommended at 4 to 6 years of age.[73] Tdap boosters should be administered at 11 to 12 years of age, and Td boosters every 10 years thereafter.[93] A single dose of combined MMR vaccine at 12 to 15 months or older provides long-lasting, probably lifelong, immunity to measles in 93% of recipients. The second dose of MMR at 4 to 6 years of age should provide immunity to almost all children not protected by the first dose.[40,156] There is no contraindication to giving DTaP, MMR, Hib, hepatitis B, polio, pneumococcal conjugate, rotavirus, hepatitis A, influenza, and varicella vaccines with any of the other vaccines. Although all potential simultaneous administration schemes have not been evaluated, experience to date suggests that simultaneous administration of most vaccines does not increase reaction rates or interfere with the immune responses.[2,3,293,294] Hib should be given in two doses (PRP-OMP) or three doses (PRP-T) in the first year of life, followed by a booster dose at 12 to 15 months of age.[50,73] Hepatitis B vaccine should be initiated at birth, and the three-dose series should be completed by 18 months of age; hepatitis B vaccine can be given simultaneously with all other childhood vaccines.[15] Combination vaccines containing hepatitis B are not licensed for use before 6 weeks of age. PCV should be administered in a four-dose series, with the first three doses administered at 2, 4, and 6 months of age and the fourth dose at 12 to 15 months. Children should receive the first dose of varicella vaccine routinely at 12 to 18 months of age.[57] Annual influenza vaccine is recommended for everyone aged 6 months or older without contraindications.[6] Children aged 6 months through 8 years receiving influenza vaccine for the first time should have two doses separated by at least 4 weeks. Children aged 6 months through 8 years who have not received at least two doses in previous seasons should receive two doses separated by 4 weeks. A table that shows all the available influenza vaccines is shown in Chapter 165 and can be found at www.cdc.gov/flu/protect/vaccine/vaccines.htm.

The newest vaccine recommendations for young children involve rotavirus vaccine, varicella vaccine, and hepatitis A vaccine. There are two rotavirus vaccine preparations. Bovine rotavirus vaccine (RV5) should be given as a three-dose series at 2, 4, and 6 months of age, and human attenuated rotavirus vaccine (RV1) should be administered in a two-dose series at 2 and 4 months of age. For both vaccines, the first dose should be given at 6 to 14 weeks (maximum, 14 weeks, plus 6 days) of age. Vaccination should not be initiated for infants aged 15 weeks, 0 days or older. The final dose in the series should be given by 8 months, 0 days of age. All children should receive two doses of varicella vaccine, the first at 12 to 18 months of age and the second at 4 to 6 years of age. Hepatitis A vaccine should be given as a two-dose series, with the first dose given at 12 to 23 months of age and the second at least 6 months later. The minimum age for the first dose is 6 months of age.

Adolescents

An adolescent preventive medicine visit has been established at 11 to 12 years of age.[73] A booster dose of Tdap should be administered to adolescents who completed the recommended childhood DTP/DTaP vaccination series and have not received a Td booster dose. The HPV vaccine series should be administered to girls and boys 11 to 12 years of age. For those not previously fully vaccinated, catch-up vaccination is recommended throughout adolescence to 18 years of age. MenACWY should be administered at 11 to 18 years of age. A single dose of vaccine should be administered at age 11 or 12 years, and a booster dose should be administered at age 16 years. Adolescents who receive their first dose at age 13 to 15 years should receive a booster dose at age 16 to 18 years. For adolescents not vaccinated prior to their 16th birthday, one routine dose is recommended after the 16th birthday. Another dose is not recommended unless a risk factor develops, such as the onset of a medical condition, travel, or occupational consideration. When further boosters are indicated, they should be administered 5 years after the prior dose. Serogroup B meningococcal vaccine may be administered to adolescents and young adults aged 16 to 23 years, with a preference for the 16- to 18-year age range. Influenza vaccine should be administered annually through adolescence and adulthood. A second dose of MMR should be administered if not previously received. Completion of the two-dose varicella vaccine series should occur at that time if the adolescent is susceptible. The three-dose hepatitis B vaccination series should be administered if not previously received. The polio immunization history should be reviewed and catch-up vaccination performed, if a full series was not previously received, through age 17 years. Other immunizations, including pneumococcal and hepatitis A, should be given if indicated.

Adults

Routine immunizations for adults have received increasing attention in recent years, with recognition of the large burden of vaccine-preventable diseases in this age group. Two adult immunization schedules have been published each year since 2002. One focuses on vaccines needed by age group, and the second focuses on vaccines needed for persons aged 19 years and older, based on 10 medical and other indications (see Figs. 316.2 and 316.3). All adults should be immune to diphtheria and tetanus and, if not previously immunized, should be given a primary immunizing course (three doses of Td administered at time zero, 4 to 8 weeks, and 6 to 12 months), with boosters administered every 10 years thereafter.[93] A one-time dose of Tdap for adults aged 19 years or older should replace one of the Td booster doses. HPV vaccine is recommended for all girls and young women 11 to 26 years of age who have not completed the immunization series. A complete series consists of three doses for adults who began the series after the 15th birthday. The second dose should be given 2 months after the first dose, and the third dose should be given 6 months after the first dose. All females from adolescence to 26 years of age should receive a complete series of HPV vaccine. Previous doses can be counted toward a complete series even if they are not the current 9vHPV vaccine (i.e., 2vHPV or 4vHPV). If vaccination was not previously performed, HPV is recommended for all boys and young men 11 to 21 years of age and for all men 22 to 26 years of age with the following conditions: MSM, HIV positive, or immunosuppressed. Providers may give HPV vaccine to all men 22 to 26 years of age.

All adults without evidence of immunity to varicella should receive two doses of single-antigen varicella vaccine 4 weeks apart if not previously vaccinated (or the second dose if they have received one dose), unless they have a medical contraindication. Special consideration should be given to adults who (1) have close contact with persons at high risk for severe disease (e.g., health care personnel and family contacts of persons with immunocompromising conditions) or (2) are at high risk for exposure or transmission (e.g., teachers, child care employees, residents and staff members of institutional settings [including correctional institutions], college students, military personnel, adolescents and adults living in households with children, nonpregnant women of childbearing age, and international travelers). Evidence of immunity to varicella in adults includes any of the following[57]: (1) documentation of two doses of varicella vaccine at least 4 weeks apart; (2) birth in the United States before 1980 (although for health care personnel and pregnant women, birth before 1980 should not be considered evidence of immunity); (3) history of varicella based on diagnosis or verification of varicella by a health care provider (for a patient reporting a history of or presenting with an atypical case, a mild case, or both, health care providers should seek an epidemiologic link with a typical varicella case or a laboratory-confirmed case or evidence of laboratory confirmation, if performed at the time of acute disease); (4) history of herpes zoster based on health care provider diagnosis or verification of herpes zoster by a health care provider; or (5) laboratory evidence of immunity or laboratory confirmation of disease.

Persons aged 50 years old or older who are immunocompetent should receive two doses of RZV, separated by 2 to 6 months, regardless of history of varicella vaccination, ZVL vaccination, chickenpox, or zoster. Persons with chronic medical conditions may be vaccinated unless their condition constitutes a contraindication. For those who have previously received ZVL vaccination, although studies were limited to a 5-year

interval between ZVL and RZV, the minimum interval from ZVL to RZV is 8 weeks based on safety considerations. For those who have not received ZVL, RZV is the preferred vaccine to ZVL.[295] Once one dose of RZV has been administered, ZVL is no longer indicated.

For those who will not receive RZV, have not received a dose of RZV, and prefer ZVL, a single dose of zoster vaccine is recommended for immunocompetent adults aged 60 years and older, regardless of whether they report a prior episode of herpes zoster.[274] Likewise, persons with chronic medical conditions may be vaccinated unless their condition constitutes a contraindication. All adults should be immune to measles and rubella. For practical purposes, persons born before 1957 generally can be considered immune to these three diseases. All other adults should receive one or more doses of MMR unless they have a medical contraindication, documentation of one or more doses after the first birthday, or laboratory evidence of immunity. One dose of MMR vaccine is recommended for women whose rubella vaccination history is unreliable or who lack laboratory evidence of immunity. For women of childbearing age, regardless of birth year, rubella immunity should be determined, and susceptible women should be counseled regarding congenital rubella syndrome. Women who do not have evidence of immunity should receive MMR on completion or termination of pregnancy and before discharge from the health care facility. Adults born before 1957 generally are considered immune to mumps. Adults born during or after 1957 should receive two doses of MMR unless they have a medical contraindication or laboratory evidence of immunity. Influenza vaccine is recommended for routine annual administration to all adults. A yearly influenza vaccine is recommended for all adults who do not have contraindications.[6] It is recommended that pneumococcal polysaccharide vaccine be administered to elderly patients and those with specific medical or other indications.[202] This dose should follow a recommended dose of PCV (PCV13) by 1 year for otherwise healthy adults aged 65 years or older. One dose of PCV (PCV13) is recommended for adults aged 19 years and older who have the following high-risk conditions: functional or anatomic asplenia, immunosuppression (including hematologic malignancy, generalized malignancy, and immunosuppressive medications), renal disease (chronic renal failure or nephrotic syndrome), cochlear implants, or CSF leak. Hepatitis B vaccine is recommended for persons with specific medical, occupational, and behavioral indications as a three-dose series at 0, 1, and 6 months. If the combined hepatitis A and hepatitis B vaccine (Twinrix) is used, three doses are administered at 0, 1, and 6 months; alternatively, a four-dose schedule, administered on days 0, 7, and 21 to 30, followed by a booster dose at month 12, may be used.[15,59,105] For adult patients receiving hemodialysis or with other immunocompromising conditions, one dose of 40 μg/mL (Recombivax HB), administered on a three-dose schedule, or two doses of 20 μg/mL (Engerix-B), administered simultaneously or with two injections at each visit on a four-dose schedule at 0, 1, 2, and 6 months, can be used.[59] Hepatitis A vaccine is given to adults with behavioral, occupational, and other indications. Single-antigen vaccine formulations should be administered in a two-dose schedule at either 0 and 6 to 12 months (Havrix) or 0 and 6 to 18 months (Vaqta).[114] If the combined hepatitis A and hepatitis B vaccine (Twinrix) is used, administer three doses at 0, 1, and 6 months; alternatively, a four-dose schedule, administered on days 0, 7, and 21 to 30, followed by a booster dose at month 12, may be used. Meningococcal vaccine is given to adults with medical and other indications.[165] Meningococcal conjugate (MenACWY) vaccine is preferred for adults with any of the following indications: persons who were vaccinated with MenACWY previously and for whom revaccination is recommended or for whom multiple doses are anticipated; those who have functional or anatomic asplenia or persistent complement component deficiency; persons who have HIV disease; those who travel repeatedly to an area endemic for meningococcal disease; military personnel; or laboratory personnel working with meningococcus. MenACWY also is indicated for first-year college students 19 through 21 years of age if they have not received a dose in the previous 5 years, or first-year college students aged 19 through 21 years if they live in a residence hall if they have not received a dose since their 16th birthday. For meningococcal-naïve adults older than 55 years who do not have any of the aforementioned risk factors, MPSV4 is preferred.[60] Serogroup B meningococcal vaccine may be administered to persons aged 16 to 23 years of age.

Special Circumstances

Travel

Persons travel internationally for business, tourism, and education and to visit relatives and friends (see Chapter 318). The two major categories of immunizations to consider for international travelers are status of the routinely recommended immunizations (see Figs. 316.1A–B, 316.2, and 316.3) and the need for specific immunizations. Specific travel immunizations should be based on evidence of benefits and risks and on expert opinion when few or no data are available. Immunizations for international travel may be grouped into two categories: *required* (those that may be required in order to cross international borders) and *recommended* (those recommended according to risk for infection in the area of travel). Country-specific immunization recommendations are available for all countries (www.cdc.gov/travel and www.who.int/ith/en). The International Health Regulations allow countries to impose requirements for yellow fever vaccine as a condition for admission.[296] Consequently, travelers should be aware of whether this vaccine is required for entry into the country of their destination. Other vaccines commonly considered for travelers include measles- and rubella-containing vaccines, polio vaccine, and boosters for tetanus and diphtheria. In addition, travelers to specified areas or seasonally may wish to consider influenza, typhoid, rabies, JE, hepatitis A, hepatitis B, cholera, and meningococcal vaccines. Information on vaccines recommended for travel is summarized regularly in *Health Information for International Travel* (www.cdc.gov/travel/contentYellow-Book.aspx). Information on specific regions and diseases is available from the CDC at www.cdc.gov/cdc-info/requestform.html.

Occupational Exposure

A complete set of recommendations for vaccination for most occupational groups has not been developed. Specific recommendations are available for health care professionals.[297] Federal regulations require that health care and public safety workers who anticipate exposure to human blood or blood-derived body fluids must be offered hepatitis B vaccination at no charge.[111] Transmission of rubella in medical facilities can occur to or from health care professionals. Consequently, it is important that all health care professionals who might transmit rubella to pregnant patients be immune against rubella. Documentation of a single dose of a rubella-containing vaccine on or after the first birthday or serologic evidence of immunity is acceptable. Health care personnel are at greater risk from measles than the general public. All health care personnel should be immune, defined as documentation of receipt of two doses of live measles vaccine on or after the first birthday, at least 1 month apart, or serologic evidence of immunity. Although most persons born before 1957 have been considered to be immune to measles, about 4% of cases in health care professionals in the past occurred in persons born before this date. Mumps transmission in health settings has rarely been reported, and mumps immunity can be ensured at the same time as measles and rubella through use of MMR vaccine.[156,173] Therefore, facilities should recommend two doses of MMR vaccine in an outbreak setting and should consider two doses in any circumstance for health care providers, regardless of their date of birth. Because health care professionals caring for patients with chronic diseases may transmit influenza to their patients, all health care professionals should be vaccinated against influenza annually.[6] Health care professionals also should be immune to varicella.[57] Those without evidence of immunity to varicella should receive two doses of single-antigen vaccine if not vaccinated previously or the second dose if they have received only one dose, unless medically contraindicated.[57] Regardless of age, health care professionals should receive a single dose of Tdap as soon as feasible if they have not previously received Tdap and regardless of the time since their most recent Td vaccination. Vaccinating health care professionals with Tdap will protect them against pertussis and is expected to reduce transmission to patients, other health care professionals, household members, and persons in the community.

Pregnancy

Because of relative lack of efficacy and safety studies of vaccines in pregnant women, many recommendations for vaccine use in pregnancy are based on disease burden and severity for mothers and infants, studies

from other countries, and expert opinion. The only vaccines recommended routinely in the United States for pregnant women are tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap), and IIVs or RIVs. Transfer of maternal antibodies to tetanus toxin is an important means of preventing neonatal tetanus. Transfer of maternal antibodies to pertussis as a means of preventing infant pertussis is accomplished optimally if the mother is vaccinated early in the interval between 27 and 36 weeks' gestation in every pregnancy. Tdap can be administered without regard to interval from the last Td or Tdap.[71] IIV should be administered to all women who will be pregnant during the influenza season, regardless of trimester. Influenza immunization of women during pregnancy not only protects the pregnant woman but also appears to protect infants younger than 6 months.[298] Infants younger than 6 months cannot be immunized or receive antiviral prophylaxis because no products are licensed for this age group. LAIV is not licensed for use in pregnant women and should not be administered. However, pregnant women do not need to avoid contact with persons immunized with LAIV. In general, live-virus vaccines are contraindicated in pregnancy, with the exception of yellow fever virus vaccine and live cholera vaccine, which may be administered if the risk for exposure to the disease during international travel is great. If indicated, some inactivated vaccines, such as hepatitis B, MenACWY (preferred, but MPS4 is acceptable), hepatitis A, and PPSV23, can be administered to pregnant women with medical or exposure conditions that put them at risk for these vaccine-preventable infectious diseases. ACIP recommendations for pregnant women can be found at www.cdc.gov/vaccines/pregnancy/hcp/guidelines.html.

Immunocompromised States

Immunocompromised persons (from primary or secondary immune deficiency conditions) are susceptible to many infections, may be more susceptible to adverse effects from live-virus vaccines,[51,64] and may respond poorly to inactivated vaccines. Consequently, in general, live-virus vaccines are not administered to immunocompromised persons, although inactivated vaccines are safe and are generally indicated.[2] IIV should be withheld from patients receiving induction chemotherapy, consolidation chemotherapy, or anti–B-cell antibodies.[299] Varicella vaccine is contraindicated in persons with most deficiencies of cell-mediated immunity but can be safely given to persons with deficiencies of humoral immunity. Recommendations for vaccination of persons with specific immunocompromising conditions have been summarized (e.g., recipients of HSCTs[2] or solid organs)[300–302] and are provided on the CDC website at http://www.cdc.gov/vaccines/spec-grps.html#conditions. The efficacy of inactivated vaccines in immunocompromised persons may be less than that in healthy persons, although inactivated vaccines are safe and indicated for many patients.[303,304] In addition, household contacts of patients with immunocompromised conditions should be immunized appropriately, including annual influenza vaccine, to reduce risk for exposure of immunocompromised persons.

Human Immunodeficiency Virus

Live-attenuated vaccines generally are contraindicated in immunocompromised persons, including persons with symptomatic HIV infection. Limited studies in HIV-infected persons generally have failed to show an increased risk for adverse events from live or inactivated vaccines. Exceptions include BCG given to patients with AIDS and measles-containing vaccine in patients with severe immunodeficiency.[305–307] Known susceptible HIV-infected children aged 8 years or younger who are asymptomatic may be considered for varicella vaccines if $CD4^+$ percentage is greater than or equal to 15%. Persons older than 8 years may be considered for varicella vaccine if their $CD4^+$ lymphocyte count is greater than or equal to 200 cells/μL. Known susceptible HIV-infected children who do not have evidence of severe immunodeficiency should receive MMR vaccine. Absence of severe immunodeficiency is defined as individuals aged 5 years or younger who have CD4 T-lymphocyte percentages greater than or equal to 15% for 6 months' duration, and individuals aged 6 years or older with CD4 T-lymphocyte percentages greater than or equal to 15% *and* CD4 cell counts greater than or equal to 200 lymphocytes/mm^3. If only percentages or counts are available, the value that is available should be used. If a child aged 5 years or younger has only CD4 counts (and not percentages) available, absence of severe immunosuppression is defined as CD4 counts less than or equal to 750 cells/mm^3 for infants, or CD4 counts less than or equal to 500 cells/mm^3 for children aged 1 through 5 years. Known susceptible HIV-infected adults who are asymptomatic should receive live-attenuated MMR vaccine if they do not have evidence of severe immunosuppression, defined as $CD4^+$ percentages greater than or equal to 15% and $CD4^+$ counts greater than or equal to 200 lymphocytes/mm^3 for 6 or more months. If only one laboratory parameter is available, the designation for immunosuppression can be made on the basis of that sole parameter. Persons with HIV infection should not receive zoster vaccine. Because of reports of severe measles disease, including death, in symptomatic HIV-infected children and adults, MMR vaccine should be considered with caution for symptomatic HIV-infected persons.[156,308] For children with perinatal HIV infection who may have received prior doses of MMR and have since received combination antiretroviral therapy, revaccination should occur with MMR vaccine.[157] MMR and varicella vaccines are contraindicated in persons with severe immunodeficiency. Recommendations from the CDC, National Institutes of Health (NIH), and Infectious Diseases Society of America (IDSA) for administration of vaccines for adults are available.[309] Although transient increases of HIV in the blood of patients have been documented in the month after receipt of both pneumococcal and influenza vaccines, their clinical significance is unknown. Adults with HIV infection who meet the age requirements and lack evidence of immunity (lack documentation of immunization or with no evidence of prior infection) should be immunized with Td/Tdap, influenza (annually), PCV13, PPSV23, MMR, MenACWY, and hepatitis B vaccine, and may be considered for vaccination with varicella vaccine. Women younger than 27 years should receive HPV vaccine. If specific risk factors are present, hepatitis A vaccine should be considered. Although a protective immune response to vaccines and toxoids cannot be ensured in these patients, some protection may be provided. A publication from the CDC, NIH, and IDSA titled "Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents" is available (http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf).

Postexposure Immunization

For certain diseases, administration of an IG product soon after exposure can prevent or attenuate expression of disease.[310] Passive prophylaxis using various IG preparations has been discussed previously. Persons who have received a complete course of immunization against tetanus are, in general, well protected against development of tetanus, particularly if a booster dose has been administered within 10 years. More problematic is the situation with persons who cannot recall their immune status or who have not been immunized. Table 316.5 shows the ACIP-recommended approach to PEP of tetanus. In addition to passive prophylaxis, there is evidence that administration of measles vaccine within 6 days after exposure may prevent manifestations of illness.[311] If the exposure did not result in infection, the vaccination should provide protection against future exposure. Varicella vaccine prevents varicella infection in exposed persons if administered within 3 to 5 days of exposure.[57,312,313] Hepatitis A vaccine and hepatitis B vaccine are other vaccines used for PEP.

Other Considerations

Storage and Handling of Vaccines

Inattention to vaccine handling and storage conditions can contribute to vaccine failure.[2,314] Live-virus vaccines, including MMR, MMRV, varicella, yellow fever, LAIV, rotavirus, and OPV vaccines, are sensitive to increased temperature (heat-sensitive). Inactivated vaccines may tolerate limited exposure to elevated temperatures but are damaged rapidly by freezing (cold sensitive). Exposure of inactivated vaccines to freezing temperature (0°C [32°F] or colder) is the most common storage error. Examples of cold-sensitive vaccines include DTaP and tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccines; IPV vaccine (particularly if adjuvanted in the combination form Pediarix); Hib vaccine; pneumococcal polysaccharide and conjugate vaccines; hepatitis A and hepatitis B vaccines; IIV; and meningococcal polysaccharide and conjugate vaccines. Some vaccines must be protected from light. Physical appearance is not an appropriate basis for determining

whether a vaccine has lost its potency because of inappropriate storage or handling. All personnel responsible for handling vaccines in an office or clinic setting should be familiar with standard procedures designed to minimize risk for vaccine failure. Recommendations for handling and storage of selected biologics are summarized in several areas, including the package insert for each product and in a web-based toolkit (www.cdc.gov/vaccines/recs/storage/default.htm). The most current information about recommended vaccine storage conditions and handling instructions can be obtained directly from manufacturers. Their telephone numbers are listed in product labels (package inserts) and in the *Physicians' Desk Reference,* which is published yearly.

Assessing the Need for Immunization

Immunization traditionally has been viewed as the task of the pediatrician and general practitioner caring for children, but with licensure of new vaccines (Tdap, MCV4, HPV, herpes zoster virus [RZVand ZVL]) and expansion of vaccine recommendations (MMR, MMRV), physicians who care for adolescents and adults should be aware of current recommendations. Health care providers should assess the immunization status of their patients at first contact and, depending on immunization status and age, at selected contacts thereafter. In general, persons should be viewed as susceptible unless they can prove immunity through documentation of having received vaccine, laboratory evidence of vaccine-induced or disease-induced immunity, or, for some diseases (e.g., hepatitis A, hepatitis B), documentation of physician-diagnosed disease, which typically includes laboratory results documenting laboratory evidence of disease-induced immunity.

A significant proportion of elderly adults in the United States have never been immunized against tetanus or diphtheria. This is reflected in the fact that 30% of the 233 cases of tetanus in the United States in the period 2001 to 2008 occurred in persons aged 65 years or older.[315] Health care professionals caring for adults, especially elderly patients, should be particularly attuned to the need for administering tetanus and diphtheria toxoids to elderly persons, with one dose given as Tdap if Tdap has not been administered previously. Similarly, studies repeatedly demonstrate that less than 70% of persons aged 65 years or older receive influenza immunization in a given year or have ever received pneumococcal vaccine.[316] It is vital that all health care professionals remind themselves and their patients of the need for annual influenza immunization of all persons aged 6 months or older.

Substantial progress has been made in implementing hepatitis B vaccination programs for children and adolescents. Progress also has been made in immunizing adults with risk factors for HBV infection.

Immunization Records

In 2002 the National Vaccine Advisory Committee (NVAC) issued revised immunization standards that included recommendations that immunization of patients be documented through use of immunization records that are accurate, complete, and easily accessible. The standards also recommend use of tracking systems to provide reminder-recall notices when immunizations are due or overdue. Immunization information systems (IISs) address record-keeping needs and tracking functions and have additional capabilities (www.cdc.gov/vaccines/programs/iis/index.html). Every person should have an immunization record that is up to date and that contains information about each dose of vaccine received, including the date.[2] Patients should be asked to bring this record with them to all health care visits, and the record should be reviewed to ensure that it is current. Official immunization record cards or some form of personally accessible electronic record should be used. The National Childhood Vaccine Injury Act requires that all providers of vaccines covered by the program (i.e., listed on the vaccine injury table, www.hrsa.gov/sites/default/files/hrsa/vaccine-compensation/vaccine-injury-table.pdf) record on the patient's permanent medical record (housed in the provider-based record system) the date, manufacturer, and lot number of each dose of vaccine administered and the name of the person administering the vaccine.[289,318] It is prudent to record the same information for other vaccines as well. An updated version of the NVAC standards has been posted at www.cdc.gov/vaccines/hcp/adults/for-practice/standards/index.html.

Every physician should ensure that the immunization record of each patient is maintained in a permanent, confidential manner that can be reviewed and updated easily, whether the record is in hard copy or electronic health record format. The format of all records should facilitate identification and recall of patients in need of immunization.

Parent and Patient Education

All patients (or their parents or guardians) should be informed of the benefits and risks associated with vaccination.[314] The discussion should be conducted in language that is comprehensible to the recipient (or parent or guardian), and ample opportunity for questions and discussion should be given. Vaccine Information Statements (VISs) have been developed for all vaccines routinely recommended for children and adults and are available in several languages. The National Childhood Vaccine Injury Act requires physicians administering vaccines covered by the Vaccine Injury Compensation Program, whether purchased with private or with public funds, to provide the relevant VIS at the time of each immunization. In addition, the Public Health Service has developed forms that explain benefits and risks of vaccination with other vaccines. Interested health care providers can receive copies of these forms through local health departments or from the Internet (www.cdc.gov/vaccines/hcp/vis/index.html and www.cdc.gov/vaccines/parents/index.html).

Simultaneous Administration and Intervals Between Immunizations

Most vaccines can be given safely and effectively at the same time.[2] In general, inactivated vaccines can be administered simultaneously at separate sites, and field observations indicate that simultaneous administration of the most widely used live-virus vaccines has not resulted in impaired antibody responses or increased rates of adverse reactions.[293] When vaccines are administered simultaneously, they should be given in separate limbs. When this is not feasible, they should be separated by at least 1 to 2 inches. However, simultaneous administration of IG and MMR-containing vaccines should be avoided because this may result in interference with antibody responses. With those vaccines, IG should not be given for at least 2 weeks after vaccination. Persons receiving high doses of IG or other blood products may have impaired responses to vaccines for as long as 11 months, depending on the dose received.[2,286] Persons who receive standard doses of IG for hepatitis A prophylaxis should wait to receive live vaccines until 3 months after IG, whereas persons treated with varicella-zoster IG should wait 5 months. Children treated for Kawasaki disease with IGIV at a dose of 2 g/kg should not be vaccinated until 11 months after the dose. Similar recommendations apply to varicella vaccine. IG does not appear to interfere with the response to yellow fever vaccine, LAIV, zoster vaccine, or rotavirus vaccines.[318] In general, the antigenic content of inactivated vaccines is so great that IG will not interfere with the antibody response.

With live vaccines, there is the theoretical possibility of interference in development of antibody responses when live vaccines are administered at intervals of 3 to 14 days. If more than one live vaccine is needed, the vaccines should be administered simultaneously or at intervals of about 1 month between different vaccines.[2] In general, there are no restrictions on intervals between doses of different inactivated vaccines or between different inactivated and live vaccines. Exceptions are the PCV13 and PPSV23 vaccines, which require an interval between them, as described in the previous discussion of these vaccines. Another exception is MenACWY-D and PCV13 in a child with functional and anatomic asplenia. Children with this condition are at high risk of disease from both of these bacteria, yet pneumococcal infection is more common, and studies show that simultaneous vaccination reduces the immunogenicity of PCV13. Therefore, if both vaccines are indicated PCV13 should be given first, followed by MenACWY-D 4 weeks later.[60] A third exception is MenACWY-D and DTaP. If DTaP has been administered, providers should administer MenACWY-D at the same time, or wait 6 months before administering MenACWY-D.

Combination Vaccines

The routine immunization schedule has become increasingly complex over the years as more vaccines have been added. Currently, all children

TABLE 316.6 FDA-Licensed Combination Vaccines

VACCINE[b]	TRADE NAME (YEAR LICENSED)	AGE GROUP	FDA LICENSURE RECOMMENDATIONS
HepA-HepB	Twinrix (2001)	≥18 yr	Three doses on a 0-, 1-, and 6-mo schedule
DTaP-HepB-IPV	Pediarix (2002)	6 wk to 6 yr	Three-dose series at 2, 4, and 6 mo of age
MMRV	ProQuad (2005)	12 mo to 12 yr	Two doses 28 days apart, on or after the first birthday
DTaP-IPV	Kinrix (2008)	4–6 yr	Booster for fifth dose DTaP and fourth dose IPV
DTaP-IPV/Hib	Pentacel (2008)	6 wk to 4 yr	Four-dose series at 2, 4, 6, and 15-18 mo of age
DTaP-IPV	Quadracel (2015)	4–yr	Booster for fifth dose DTaP and fourth or fifth dose IPV

[a]Excludes MMR, DTaP, Tdap, and IPV, for which single-antigen products are not available in the United States.
[b]Hyphen (-) indicates that products' active components are supplied in their final form by the manufacturer and do not require mixing or reconstitution by user; slash (/) indicates that products' active components are mixed or reconstituted by user.
DTaP, Diphtheria and tetanus toxoids and acellular pertussis vaccine; *FDA,* US Food and Drug Administration; *HepA,* hepatitis A vaccine; *HepB,* hepatitis B vaccine; *IPV/Hib,* trivalent inactivated polio vaccine and *Haemophilus influenzae* type b vaccine; *MMR,* measles-mumps-rubella vaccine; *MMRV,* measles-mumps-rubella and varicella vaccine; *Tdap,* tetanus, diphtheria, and acellular pertussis (adult) vaccine.
Modified from American Academy of Pediatrics. Active immunization. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS, eds. Red Book: 2009 Report of the Committee on Infectious Diseases. *28th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2009:1–55; Centers for Disease Control and Prevention (CDC). Notice to readers. FDA approval for infants of a* Haemophilus influenzae *type b conjugate and hepatitis B (recombinant) combined vaccine.* MMWR Morb Mortal Wkly Rep. *1997;46:107–109; CDC. FDA approval of a* Haemophilus *b conjugate vaccine combined by reconstitution with an acellular pertussis vaccine.* MMWR Morb Mortal Wkly Rep. *1996;45:993–995; CDC. Notice to readers: FDA approval for a combined hepatitis A and B vaccine.* MMWR Morb Mortal Wkly Rep. *2001;50:806–807; CDC. Notice to readers. FDA licensure of diphtheria and tetanus toxoids and acellular pertussis adsorbed, hepatitis b (recombinant), and poliovirus vaccine combined, (PEDIARIX) for use in infants.* MMWR Morb Mortal Wkly Rep. *2003;52:203–204; CDC. Notice to readers. Licensure of a combined live attenuated measles, mumps, rubella, and varicella vaccine.* MMWR Morb Mortal Wkly Rep. *2005;54:1212–1214; CDC. Licensure of a diphtheria and tetanus toxoids and acellular pertussis adsorbed and inactivated poliovirus vaccine and guidance for use as a booster dose.* MMWR Morb Mortal Wkly Rep. *2008;57:1078–1079; and CDC. Licensure of a diphtheria and tetanus toxoids and acellular pertussis adsorbed, inactivated poliovirus, and Haemophilus b conjugate vaccine and guidance for use in infants and children.* MMWR Morb Mortal Wkly Rep. *2008;57:1079–1080.*

should be protected against 16 diseases. This schedule can require as many as 21 injections of various vaccines through 18 months of age and an additional 6 injections by 18 years of age (excluding influenza vaccines)—a major challenge for any health care delivery system. Influenza vaccine requires 2 injections for children younger than 9 years when they are first vaccinated and then 1 injection annually thereafter. Combination vaccines can provide equivalent protection with substantially fewer injections.[294,319–325] Vaccines combining antigens against multiple diseases have been a part of the routine immunization schedule for years.

For children and adolescents, many combination vaccines are available (Table 316.6). Combination vaccines may be used instead of their equivalent component vaccines when any component is indicated for the patient's age and other components are not contraindicated as licensed by the FDA. Combination vaccines represent an opportunity to reduce the number of injections. Table 316.6 shows combination vaccines licensed for use in the United States and recommendations for administration.

For adults, combination hepatitis A and hepatitis B vaccine (Twinrix) is available as a three- or four-dose regimen. This vaccine can be administered at 0, 1, and 6 months or, alternatively, at days 0, 7, and 21 to 30, followed by a booster dose at month 12.

Data suggest that MMRV, because it is associated with a higher risk for fever than administration of MMR and varicella simultaneously at different sites, also may cause an increased risk for febrile seizures after the first dose of the two-dose series.[161] In June 2009, after consideration of the postlicensure data and other evidence, ACIP adopted new recommendations regarding use of MMRV vaccine for the first and second doses and identified a personal or family (i.e., sibling or parent) history of seizure as a precaution for use of MMRV vaccine. For the first dose of measles, mumps, rubella, and varicella vaccines at age 12 to 47 months, either MMR vaccine and varicella vaccine or MMRV vaccine may be used. Providers who are considering administering MMRV vaccine should discuss the benefits and risks of both vaccination options with the parents or caregivers. Unless the parent or caregiver expresses a preference for MMRV vaccine, the CDC recommends that MMR vaccine and varicella vaccine be administered for the first dose in this age group. For the second dose of measles, mumps, rubella, and varicella vaccines at any age (15 months to 12 years) and for the first dose at age 48 months or older, use of MMRV vaccine generally is preferred over separate injections of its equivalent component vaccines (i.e., MMR vaccine and varicella vaccine). For persons aged 48 months or older, MMRV is usually preferred for the first dose if vaccination against varicella is also needed.

Interrupted Schedules

Immunologic memory induced by vaccines is usually long-term. Therefore, when one or more doses in a schedule of multiple doses are missed, there is no need to restart the series. Instead, continue from where the schedule stopped.

Reporting of Disease and Adverse Events

Public health officials at state health departments and the CDC collaborate in determining which diseases should be nationally notifiable. A disease may be added to the list as new pathogens emerge or may be deleted as the incidence decreases. Reporting of national notifiable diseases to the CDC by states is voluntary. Reporting is mandated by legislation or regulation by individual states. The list of reportable diseases (www.cdc.gov/nndss) includes many diseases preventable through vaccination. Health care providers should ensure that each suspected case of vaccine-preventable disease is reported promptly to the local or state health department. Similarly, certain adverse events after immunization should be reported to the Vaccine Adverse Event Reporting System (VAERS). These include any adverse event listed by the manufacturer as a contraindication to further doses of the vaccine, or any adverse event listed in the VAERS Table of Reportable Events Following Vaccination (https://vaers.hhs.gov/resources/infoproviders.html) In addition, CDC encourages reporting of any clinically significant adverse event that occurs in a patient following a vaccination, even if the provider is unsure whether a vaccine caused the event. VAERS reports can be submitted online (http://vaers.hhs.gov). Forms for VAERS can also be obtained by calling 800-822-7967 if Internet access is not available. The National Childhood Vaccine Injury Act requires providers to report specified adverse events if they occur within a designated time frame after immunization.[318,326] Only through accurate reporting and follow-up of both disease and adverse vaccine effects can the changing balance of the benefits and risks of vaccination be properly assessed.

Compensation for Vaccine Injuries

The National Childhood Vaccine Injury Act of 1986 established a no-fault compensation program for persons injured by vaccines.[317,318] The covered vaccines, adverse events, and time intervals for which persons are eligible for compensation in the absence of other known causes for the events can be found at www.hrsa.gov/vaccinecompensation/. All persons with alleged injuries from covered vaccines must file first under the compensation program. Those who meet the criteria of the table

(and other legal requirements) are entitled to compensation without proving that vaccine caused the injury. Persons alleging a condition not included in the table or who otherwise do not meet criteria in the table must prove that the vaccine was the cause. Persons may accept decisions of the program or reject those decisions and go to the tort system. If compensation decisions are accepted, manufacturers and vaccine administrators are protected from litigation.[317,318] More information on the compensation program can be obtained by calling 800-338-2382 or through the Division of Vaccine Injury Compensation's home page (www.hrsa.gov/vaccinecompensation/).

Standards for Immunization Practices

To improve the quality of immunization delivery, standards for child and adolescent immunization practices and standards for adult immunization practices have been developed by the NVAC (Tables 316.7 and 316.8).[327] These standards seek to minimize missed opportunities for immunization, ensure that appropriate contraindications are observed, and ensure that prospective vaccinees or their parents are adequately educated about vaccine risks and benefits. In addition, the standards include other measures to enhance the safe and effective use of vaccines.

Some of the more critical standards include providing vaccines in all health care settings; minimizing prevaccination requirements such as physician evaluation when those services are not readily obtainable; screening for contraindications, including, at a minimum, observation of the child, soliciting illness history from the parents, and verbally asking questions about contraindications; use of simultaneous immunization except when, in the judgment of the provider, nonsimultaneous vaccination will not compromise the immunization status of the patient; providing valid information on vaccine benefits and risks; and performing regular audits of patient records to determine the vaccination levels of the patients in each provider's practice. These standards are listed at www.hhs.gov/nvpo/nvac/index.html. Valid contraindications can be viewed at www.cdc.gov/vaccines/hcp/acip-recs/general-recs/contraindications.html.

The IDSA has established 46 guidelines that combine relevant aspects of both the pediatric and the adult standards.[314]

TABLE 316.7 Standards for Child and Adolescent Immunization Practices

Availability of Vaccines

1. Vaccination services are readily available.
2. Vaccinations are coordinated with other health care services and provided in a medical home when possible.
3. Barriers to vaccination are identified and minimized.
4. Patient costs are minimized.

Assessment of Vaccination Status

5. Health care professionals review the vaccination and health status of patients at every encounter to determine which vaccines are indicated.
6. Health care professionals assess for and follow only medically accepted contraindications.

Effective Communication About Vaccine Benefits and Risks

7. Parents/guardians and patients are educated about the benefits and risks of vaccination in a culturally appropriate manner and in easy-to-understand language.

Proper Storage and Administration of Vaccines and Documentation of Vaccinations

8. Health care professionals follow appropriate procedures for vaccine storage and handling.
9. Up-to-date, written vaccination protocols are accessible at all locations where vaccines are administered.
10. Persons who administer vaccines and staff members who manage or support vaccine administration are knowledgeable and receive ongoing education.
11. Health care professionals simultaneously administer as many indicated vaccine doses as possible.
12. Vaccination records for patients are accurate, complete, and easily accessible.
13. Health care professionals report adverse events after vaccination promptly and accurately to the Vaccine Adverse Event Reporting System (VAERS) and are aware of a separate program, the National Vaccine Injury Compensation Program (VICP).
14. All personnel who have contact with patients are appropriately vaccinated.

Implementation of Strategies to Improve Vaccination Coverage

15. Systems are used to remind parents, guardians, patients, and health care professionals when vaccinations are due and to recall those who are overdue.
16. Office- or clinic-based patient record reviews and vaccination coverage assessments are performed annually.
17. Health care professionals practice community-based approaches.

From National Vaccine Advisory Committee. Standards for Child and Adolescent Immunization Practices. Pediatrics. *2003;112:958–963.*

Methods to Improve Immunization Coverage

The Task Force on Community Preventive Services has reviewed the literature carefully to determine effective interventions to improve immunization coverage for children, adolescents, and adults.[328] Provider-based interventions have been some of the most successful.[329] Some of the more important include use of standing orders; assessment of immunization levels in a given practice, with provision of information back to the provider; and use of reminder-recall systems.[329–331]

A review of studies of standing orders for improving immunization uptake documented 27 studies of adults that demonstrated a median increase of 24 percentage points (interquartile interval: range, 12–35 percentage points). Four studies with children demonstrated a median absolute percent increase of 28 percentage points (range, 8–49 percentage points). These data can be found at www.thecommunityguide.org/vaccines/RRstandingorders.html.

Studies have shown that providers (as well as parents) tend to overestimate the level of coverage in their patients (or children), and formal review of records can be useful in making practitioners aware of the need to continue to pay attention.[328–330] Bushnell asked physicians and nurses from both public and private sectors in Massachusetts to estimate immunization coverage of their patient populations. Estimates ranged from 85% to 100%. Record reviews documented a median coverage of 61% (range, 19%–93%).[331] Giving this information back to providers has been shown to lead to improvements in coverage.[332]

Reminder systems entail providing reminders to patients and parents or providers that an individual is due for an immunization. Recall systems notify individuals that they are past due for an immunization. Both patient and provider reminder-recall systems have been studied extensively and demonstrated to be effective.[329] ACIP, AAP, and AAFP have recommended "the regular use of R-R (reminder-recall) systems by public and private health-care providers in settings that have not achieved high documented levels of age-appropriate vaccinations."[307]

IISs, sometimes called immunization registries, can automate assessment, reminder and recall, and a number of other activities, such as assisting the practitioner in deciding whether a vaccine is needed, consolidating multiple records into a single complete record for a given individual, generating immunization records, and generating immunization coverage information for reports, such as those called for in managed care settings by the Health Plan Employer Data Information Set.[334] Registries increasingly are being developed and used throughout the United States, and there is a Healthy People 2020 objective to "increase the percentage of children younger than 6 years whose immunization records are in a fully operational, population-based immunization information system (IIS)" and "increase the number of states that have 80% of adolescents with two or more age-appropriate immunizations recorded in an IIS among adolescents aged 11 to 18 years."[335,336] Most of these persons are probably younger adults who participated as children.

Most public health authorities believe that a nationwide network of community-state population-based registries capable of exchanging information while maintaining privacy and confidentiality is essential to maintain the improvements in vaccine coverage that have been achieved. The Community Preventive Services Task Force "recommends immunization information systems on the basis of strong evidence of effectiveness in increasing vaccination rates" (www.thecommunityguide.org/vaccines/imminfosystems.html).

Sources of Information

Websites that provide comprehensive information on immunization are available from multiple sources listed in Pickering[314] and Wexler.[337]

TABLE 316.8 Summary of 2013 National Vaccine Advisory Committee's Standards for Adult Immunization Practices

AUDIENCE	SUMMARY OF STANDARDS
All providers	Incorporate immunization needs assessment into every clinical encounter. Strongly recommend needed vaccine(s) and either administer vaccine(s) or refer patient to a provider who can immunize. Stay up-to-date on, and educate patients about, vaccine recommendations. Implement systems to incorporate vaccine assessment into routine clinical care. Understand how to access immunization information systems (i.e., immunization registries).
Nonimmunizing providers	Routinely assess the immunization status of patients, recommend needed vaccine(s), and refer patient to an immunizing provider. Establish referral relationships with immunizing providers. Follow up to confirm patient receipt of recommended vaccine(s).
Immunizing providers	Ensure professional competencies in immunizations. Assess immunization status in every patient care and counseling encounter and strongly recommend needed vaccine(s). Ensure that receipt of vaccination is documented in patient medical record and immunization registry.
Professional health care–related organizations, associations, systems	Provide immunization education and training of members, including trainees. Provide resources and assistance to implement protocols and other systems to incorporate vaccine needs assessment and vaccination or referral into routine practice. Encourage members to be up-to-date on their own immunizations. Assist members in staying up-to-date on immunization information and recommendations. Partner with other immunization stakeholders to educate the public. Seek out collaboration opportunities with other immunization stakeholders. Collect and share best practices for immunization. Advocate policies that support adult immunization standards. Insurers, payers, entities that cover adult immunization services should ensure that their network is adequate to provide timely immunization access and augment with additional vaccine providers if necessary.
Public health departments	Determine community needs, vaccination capacity, and barriers to adult immunization. Provide access to all ACIP-recommended vaccinations for insured and uninsured adults and work toward becoming an in-network provider for immunization services for insured adults. Partner with immunization stakeholders and support activities and policies to improve awareness of adult vaccine recommendations, increase vaccination rates, and reduce barriers. Ensure professional competencies in immunizations. Collect, analyze, and disseminate immunization data. Provide outreach and education to providers and the public. Work to decrease disparities in immunization coverage and access. Increase immunization registry access and use by vaccine providers for adult patients. Develop capacity to bill for immunization of injured people. Ensure preparedness for identifying and responding to outbreaks of vaccine-preventable diseases. Promote adherence to applicable laws, regulations, and standards among adult immunization stakeholders.

ACIP, Advisory Committee on Immunization Practices.
From National Vaccine Advisory Committee. Recommendations from the National Vaccine Advisory Committee: standards for adult immunization practice. Public Health Rep. *2014;129:115–123.*

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The complete reference list is available online at Expert Consult.

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