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 respo nses.[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]