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

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

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

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

No recommendation

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

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

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

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

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

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

Delay vaccination until after pregnancy if vaccine is indicated

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

No recommendation

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

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

Notes Recommended Adult Immunization Schedule United States, 2019

Haemophilus influenzae type b vaccination

Special situations

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

Hepatitis A vaccination

Routine vaccination

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

Special situations

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

Hepatitis B vaccination

Routine vaccination

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

Special situations

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

Human papillomavirus vaccination

Routine vaccination

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

Special situations

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

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

Notes

Recommended Adult Immunization Schedule United States, 2019

Influenza vaccination

Routine vaccination

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

Special situations

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

Measles, mumps, and rubella vaccination

Routine vaccination

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

Special situations

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

Meningococcal vaccination

Special situations for MenACWY

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

Special situations for MenB

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

FIG. 316.4, cont'd

Continued

Notes Recommended Adult Immunization Schedule United States, 2019

Pneumococcal vaccination

Routine vaccination

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

Special situations

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

Tetanus, diphtheria, and pertussis vaccination

Routine vaccination

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

Special situations

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

Varicella vaccination

Routine vaccination

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

Special situations

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

Zoster vaccination

Routine vaccination

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

Special situations

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

FIG. 316.4, cont'd

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

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

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

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

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

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

Hepatitis A Vaccine

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

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

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

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

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

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

Hepatitis B Vaccine

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

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

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

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

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

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

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

Human Papillomavirus Vaccines

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Live-Attenuated Influenza Vaccine

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

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

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

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

Contraindications to LAIV include a history of severe allergic reaction to any component of the vaccine or after a previous dose of any influenza vaccine; concomitant aspirin or salicylate-containing therapy in children and adolescents; children aged 2 through 4 years who have received a diagnosis of asthma or whose parents or caregivers report that a health care provider has told them that during the preceding 12 months their child had wheezing or asthma or whose medical record indicates a wheezing episode has occurred during the previous 12 months; children and adults who are immunocompromised from any cause (including immunosuppression caused by medication or by HIV infection); close contacts and caregivers of severely immunosuppressed persons who require a protected environment; pregnancy; and receipt of an influenza antiviral medication within the previous 48 hours. Precautions regarding use of LAIV include moderate or severe acute illness or fever; history of GBS within 6 weeks of a previous dose of influenza vaccine; asthma in persons aged 5 years and older; and other underlying medical conditions that might predispose to complications after wild-type influenza infection (e.g., chronic pulmonary, cardiovascular [except isolated hypertension], renal, hepatic, neurologic, hematologic, or metabolic [including diabetes mellitus] disorders).[6]

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

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

Persons who report having had reactions to egg involving symptoms other than hives, such as angioedema, respiratory distress, lightheadedness, or recurrent emesis, or who required epinephrine or another emergency medical intervention, may similarly receive any licensed and recommended influenza vaccine (i.e., any age-appropriate IIV, RIV4, or LAIV4) that is otherwise appropriate for the recipient's age and health status. The selected vaccine should be administered in an inpatient or outpatient medical setting (including but not necessarily limited to hospitals, clinics, health departments, and physician offices). Vaccine administration should be supervised by a health care provider who is able to recognize and manage severe allergic conditions.

Japanese Encephalitis

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

Measles-Containing Vaccine

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

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

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

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

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

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

Meningococcal Vaccines

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

Conjugate meningococcal vaccines reduce carriage and induce herd protection.

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

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

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

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

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

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

Mumps Vaccine

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

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

Pertussis-Containing Vaccine

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

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

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

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

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

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

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

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

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

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

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

Plague Vaccine

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

Pneumococcal Polysaccharide Vaccine

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

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

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

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

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

Pneumococcal Conjugate Vaccine

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

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

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

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

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

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

Polio Vaccine

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

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

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