Chapter 4
Vaccine-Preventable Diseases and the Vaccines That Prevent Them

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Abbreviations

ACIP	Advisory Committee on Immunization Practices
AIDS	Acquired immune deficiency syndrome
B. anthracis	*Bacillus anthracis*
B. pertussis	*Bordetella pertussis*
C. diphtheriae	*Corynebacterium diphtheriae*
C. tetani	*Clostridium tetani*
CDC	Centers for Disease Control and Prevention
CRS	Congenital rubella syndrome
CSF	Cerebrospinal fluid
CVS	Congenital varicella syndrome
DNA	Deoxyribonucleic acid
DT	Diphtheria toxoid and tetanus toxoid
DTaP	Diphtheria toxoid, tetanus toxoid, and acellular pertussis
DTP	Diphtheria toxoid, tetanus toxoid, and whole-cell pertussis
EKG	Electrocardiogram
FDA	Food and Drug Administration

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FUTURE	Females United to Unilaterally Reduce Endo/Ectocervical Disease
H1N1	Hemagglutinin subunit one and neuraminidase subunit one
H3N2	Hemagglutinin subunit three and neuraminidase subunit two
HAV	*Hepatitis A virus*
HBV	*Hepatitis B virus*
HCC	Hepatocellular carcinoma
HepA	Hepatitis A vaccine
HepB	Hepatitis B vaccine
Hib	*Haemophilus influenzae* type b
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
HSCT	Hematopoietic stem cell transplant
IG	Immunoglobulin
IIV3	Trivalent inactivated influenza vaccine
IIV4	Quadrivalent inactivated influenza vaccine
IM	Intramuscular
IPV	Inactivated poliovirus vaccine
IV	Intravenous
LAIV	Live attenuated influenza vaccine
M. tuberculosis	*Mycobacterium tuberculosis*
MMR	Measles, mumps, rubella
MMRV	Measles, mumps, rubella, varicella
MPSV4	Menomune®
MSM	Men who have sex with men
MSW	Men who have sex with women
N. meningitidis	*Neisseria meningitidis*
OPV	Oral poliovirus vaccine
PCV13	Prevnar 13®
PCV7	Prevnar®
PEP	Postexposure prophylaxis
PHN	Postherpetic neuralgia
PPSV23	Pneumovax®
REST	Rotavirus Efficacy and Safety Trial
RNA	Ribonucleic acid
RV1	Rotarix®
RV5	RotaTeq®
S. pneumoniae	*Streptococcus pneumoniae*
S. typhi	*Salmonella typhi*
STD	Sexually transmitted disease
TB	Tuberculosis
Tdap	Tetanus toxoid, diphtheria toxoid, and acellular pertussis
V. cholerae	*Vibrio cholerae*
VZV	Varicella zoster virus

Vaccine-Preventable Diseases and the Vaccines that Prevent Them

In the following section, the 17 vaccine-preventable diseases for which routine immunization is recommended in the USA are discussed. Clinical signs and symptoms of the 17 diseases are reviewed, epidemiology and incidence is discussed, and available vaccines to prevent the 17 diseases are reviewed. The discussion progresses in the order in which the vaccines were developed.

Diphtheria

Prior to the introduction of a vaccine against it, diphtheria was a leading cause of childhood death and a common disease in the USA, with more than 200,000 cases reported during the 1920s. Approximately 5–10% of diphtheria cases were fatal, with the highest case fatality ratios recorded for the very young and the elderly. Today, diphtheria is a rare disease in the USA, primarily because of the high level of vaccination with diphtheria and tetanus toxoid and pertussis vaccine (DTP) among children as well as an apparent reduction in the circulation of toxigenic strains of the bacterium *Corynebacterium diphtheriae* (*C. diphtheriae*) [2]. A three-dose complete vaccination series substantially reduces the risk of developing diphtheria, and those that get the disease get a milder form of it. However, vaccinated persons may continue to be asymptomatic carriers of the bacteria [3]. Waning immunity puts adults at risk for the disease, and travel to endemic areas poses an additional risk factor for travelers.

Disease is caused by the protein synthesis inhibiting exotoxin from *C. diphtheriae* biotype *mitis*, *gravis*, *intermedius*, or *belfanti*. Infection is spread via respiratory droplets, direct contact, and, more rarely, by fomites. Diphtheria may be classified as either *respiratory diphtheria* or *cutaneous diphtheria.* Respiratory diphtheria disease symptoms begin with fever, malaise, and sore throat. The disease incubation period is 2–5 days. The hallmark of respiratory diphtheria is the presence of a white pseudomembrane that develops on the mucous membranes of the tonsils, soft palate, and pharynx as a result of toxin-induced necrosis of tissues. A characteristic “bull neck” from significant cervical soft tissue edema and lymphadenopathy may develop. Untreated, the highly adherent pseudomembrane may progressively extend into the larynx and trachea and cause airway obstruction, resulting in death secondary to membrane aspiration. Additionally, absorption of diphtheria toxin from the site of infection can cause systemic complications including kidney, myocardial, and neurologic damage. Case fatality rate for those infected is ~10%. Cutaneous disease, most common in the tropics, is usually mild, presenting as shallow ulcers, or nondescript sores, and rarely causes toxic complications. Since 1980, cutaneous diphtheria has not been a nationally reportable disease, but respiratory diphtheria remains reportable [4].

The most effective treatment of diphtheria is prompt antitoxin administration, available from CDC on request, and antibiotics with the patient placed in isolation [3]. *CDC Yellow Book* lists the current areas of endemicity around the world in Asia, the South Pacific, the Middle East, Eastern Europe, Haiti, and the Dominican Republic and reports large outbreaks in Indonesia, Thailand, and Laos that have occurred since 2011.

Tetanus

Clostridium tetani (*C. tetani*) is an obligate gram-positive anaerobic bacillus that forms exotoxin-producing spores that cause tetanus, or lockjaw, a life-threatening disease. The *C. tetani* spores are widely distributed in soil and in the intestines and feces of horses, sheep, cattle, dogs, cats, rats, guinea pigs, and chickens. Manure-treated soil may contain large numbers of spores. The spores can also be found in contaminated heroin and on human skin surfaces; a significant number of adults who live in agricultural areas have been found to harbor *C. tetani* [5]. Infection is commonly the result of a puncture wound or cut in the skin, but can occur with any exposure of tetanus-containing soil to an opening in the skin. Mortality rates between 10 and 80% are reported and noted to be highest in affected neonates and the elderly. Reported cases in the USA have declined by greater than 95%, and deaths from tetanus have declined by greater than 99% since 1947, when the disease became reportable nationally [6].

Tetanus is a clinical syndrome lacking confirmatory laboratory tests. It is characterized by generalized rigidity and convulsive spasms of skeletal muscles as disseminated *C. tetani* spores affect the central nervous systems, including peripheral motor end plates, the spinal cord, and the brain, and the sympathetic nervous system. Symptoms are produced when tetanus toxin interferes with release of neurotransmitters, blocking inhibitor impulses, leading to unopposed muscle contractions and spasms. Muscle stiffness usually involves the jaw (lockjaw) and neck and then becomes generalized. The most common form of the disease is generalized tetanus which includes the classic triad of trismus, muscle rigidity, and reflex spasms [7].

With the advent of tetanus toxoid vaccines and the use of tetanus antitoxin for wound management, tetanus is now uncommon in developed countries. There are currently four kinds of vaccines used today to protect against tetanus, all of which are combined with vaccines for other diseases:

- Diphtheria and tetanus (DT) vaccines
- Diphtheria, tetanus, and pertussis (DTaP) vaccines
- Tetanus and diphtheria (Td) vaccines
- Tetanus, diphtheria, and pertussis (Tdap) vaccines

Older adults over 65 years of age are at greater risk for tetanus and fatal disease than younger persons, likely due to inadequate vaccination rather than inadequate

response to vaccination. It is established that tetanus immunity wanes following childhood vaccination, leaving many adults susceptible to tetanus [6]. Therefore, continued vaccination is needed throughout the lifespan.

During 2001–2008, a total of 233 cases (an average of 29 cases/year) of tetanus were reported from 45 states with 26 reported fatal outcomes [8]. However, tetanus is still endemic in developing nations and remains an important cause of death globally, with over 250,000 deaths annually in neonates alone.

Pertussis

Whooping cough, or pertussis, is caused by the highly contagious bacteria, *Bordetella pertussis*, and is a nationally notifiable disease. Pertussis is a common, endemic disease in the USA with peaks in reported disease every 3–5 years as well as frequent outbreaks. The incidence rate of pertussis among infants exceeds that of all other age groups. The primary goal of pertussis outbreak control efforts is to decrease morbidity and mortality among infants, with a secondary goal is to decrease morbidity among all others [9].

In the absence of a more likely diagnosis, CDC defines the clinical case definition of pertussis as a cough illness lasting 2 weeks or longer with one of the following symptoms: paroxysm of coughing, inspiratory "whoop," posttussive vomiting, or apnea (with or without cyanosis) in infants aged 1 year or less. The laboratory criteria for diagnosis include the isolation of *Bordetella pertussis* from clinical specimens or positive polymerase chain reaction (PCR) for *B. pertussis*. Symptoms of pertussis usually develop within 5–10 days after exposure, but sometimes not for as long as 3 weeks after exposure.

Classically, pertussis occurs in three distinct phases: the catarrhal phase, the paroxysmal phase, and the convalescent phase. The catarrhal, or prodromal phase, lasts 1–2 weeks and consists of symptoms of typical upper respiratory tract infections, including rhinorrhea, conjunctivitis, mild cough, and low-grade fever. The paroxysmal phase is characterized by paroxysms of cough followed by sudden inspiration against a partially closed glottis. This deep inhalation creates the characteristic "whoop" for which the disease is named. This phase typically lasts 2–4 weeks, but may last up to 20 weeks. While adults may have symptoms of disease ranging from asymptomatic or mild to the typical protracted disease, infants are at high risk of severe complications, including pneumonia, apnea, and death. Severe cough paroxysms may cause sequelae including subconjunctival hemorrhage, cyanosis, hemoptysis, and hernias. Other severe sequelae include bronchopneumonia and neurologic complications. Eventually, in the convalescent stage, cough paroxysms begin to decrease in frequency and severity, though an intermittent cough may persist for months. Treatment does not significantly alter the disease course, but can decrease transmission to others [10].

Prior to vaccination, the USA experienced over 100,000 cases of pertussis annually, with nearly all persons acquiring the disease by the age of 16 (peak incidence

from 1 to 4 years of age). Post introduction of the pertussis vaccine, the numbers of annual cases decreased to just over 1000 in the 1970s. The resurgence of pertussis reported in recent years appears to be due to waning immunity. Recent estimates suggest just 10% of children remain immune to pertussis 8.5 years after their final DTaP injection [11]. Infection is primarily seen among adolescents and adults, who transmit the disease to young infants. The majority of infant infections appear to be transmitted from close household contacts, including mothers. For protection of newborns and infants, it is recommended that all pregnant women receive a Tdap booster, preferably between 27 and 36 weeks of gestational age, for transplacental antibody transfer. Additionally, CDC encourages "cocooning" an infant through vaccination of all household or other close contacts of infants with a Tdap booster.

Diphtheria, Tetanus, and Pertussis Vaccine and Vaccine Efficacy

One of the earliest recommended childhood vaccines was the combination vaccine for tetanus, diphtheria, and pertussis developed in the 1940s [12]. Diphtheria toxoid, tetanus toxoid, and whole-cell pertussis (DTP) was licensed in 1949 [13]. The components of the combination vaccines have evolved over time; the most current vaccines protecting against diphtheria toxoid, tetanus toxoid, and pertussis are provided in Table 4.1.

Clinical diphtheria and tetanus efficacy data for both Infanrix® and Daptacel® is limited to immunogenicity studies reported in manufacturer package insert. Immunogenicity demonstrated in separate studies of Infanrix® and Daptacel® was strong, with 100% of sera tested one month after three-dose primary series achieving adequate levels of diphtheria and tetanus antitoxin concentrations [14, 15]. The clinical efficacy of the diphtheria toxoid has been estimated to be 97% [19]. Unfortunately, the duration of immunity provided by primary vaccination antibody titers is thought to decrease after 8 years [20].

Clinical efficacy of DTP varied from 1938 to1983 in the USA, from 54% to 96%. Potential explanations for the wide variance in efficacies were differences in defined protection, standard of clinical diagnostic criteria, vaccine composition, and relationship between serology and protection [21]. Safety concerns with the whole-cell pertussis vaccine (convulsions, hypotonic-hyporesponsive episodes, acute encephalopathy with possible brain damage), though rare, ultimately prompted the development of acellular pertussis vaccines. In 1997, the recommendations changed from DTP (whole cell) to DTaP (acellular) for at least the first three primary doses of routine diphtheria, tetanus, and pertussis. Efficacy for DTaP vs. DTP is difficult to compare in many studies due to differences in study designs, case definitions, and laboratory methods used to confirm the diagnosis of pertussis. The efficacy of three doses of acellular pertussis vaccines was within the range expected for most whole-cell DTP vaccines, ranging from 59% to 89% [22]. Recently, the duration of immunity of DTaP has come into question, and need for earlier or repeated booster doses is under consideration. A study comparing relative risk ratios for pertussis in two

Table 4.1 Diphtheria, tetanus, and pertussis combination vaccines

Vaccine contents/ abbreviation	Trade name	FDA-approved age indication	Year approved	Notes
Diphtheria toxoid, tetanus toxoid, and acellular pertussis (DTaP)	Daptacel®[a]	6 weeks through 6 years	2002	Five-dose series
DTaP	INFANRIX®[b]	6 weeks to 7 years old	1997	
Tetanus toxoid, diphtheria toxoid, and acellular pertussis (Tdap)	Adacel®[c]	10 through 64 years old	2005	
Tdap	Boostrix®[d]	≥10 years and older	2005	
Td	Tenivac®[e]	≥7 years and older	2003	Replaced Decavac, which was discontinued in 2012

Other diphtheria, tetanus, and pertussis combination vaccines

Vaccine contents	Trade name	FDA-approved age indication	Year approved	Notes for use
DT	Generic produced by Sanofi Pasteur[f]	6 weeks through 6 years	1997	five-dose series; pediatric alternative for those that have a contraindication to the pertussis component of DTaP
DTaP + HepB + IPV	Pediarix®[g]	6 weeks through 6 years	2002	three-dose series; combination alternative
DTaP + IPV	Kinrix®[h]	4 to 6 years	2008	Single dose; combination alternative
DTaP + IPV + Hib	Pentacel®[i]	6 weeks through 4 years	2008	four-dose series; combination alternative

[a]Daptacel [Package Insert] [14]
[b]INFANRIX [Package Insert] [15]
[c]Adacel [Package Insert] [16]
[d]BOOSTRIX [Package Insert] [17]
[e]Tenivac [Package Insert] [18]
[f]Diphtheria and Tetanus Toxoids Absorbed [Package Inset] [226]
[g]Pediarix [Package Insert] [317]
[h]Kinrix [Package Insert] [318]
[i]Pentacel [Package Insert] [319]

states, 2 years and 6 years after a five-dose DTaP series, found a 2.5–4-fold increase in relative risk of pertussis 6 years after completion of five-dose DTaP primary series [23]. It is estimated that 90% of children will be susceptible to pertussis 8.5 years after last dose of DTaP series [11].

Both Adacel® and Boostrix® were approved in 2005, as Tdap boosters for adolescents over the age of ten [16, 17]. The estimated efficacy and duration of immunity to Tdap were assessed, with an efficacy of 68.8% after vaccination, declining to 8.9% by 4 or more years [24].

Influenza

Influenza causes millions of illnesses each year in the USA, resulting in thousands of hospitalizations. Depending upon the severity of the influenza season, CDC reports between 3,000 and 49,000 deaths annually from influenza infections. The overall US burden of influenza disease estimated across all age groups during the 2014–2015 season was 40 million flu illnesses, 19 million flu-associated medical visits, and 970,000 flu-associated hospitalizations [25]. Worldwide, seasonal influenza is estimated to cause severe disease in 3–5 million people, leading to 250,000–500,000 deaths annually [26].

There are three antigenic types of influenza: A, B, and C. Influenza A is further subdivided into subtypes by two of its antigenic surface proteins, hemagglutinin and neuraminidase. Influenza A viruses can undergo both antigenic shift and drift, while influenza B viruses only change by antigenic drift [27]. RNA mutations with small antigenic *drifts* occur slowly over time, necessitating the need for an updated annual influenza vaccine. Conversely, antigenic *shift* changes occur abruptly and suddenly, with gene reassortment or exchange resulting in distinct changes to the hemagglutinin and neuraminidase protein antigens. This shift may result in a brand new virulent virus and an influenza epidemic or pandemic. Influenza A is responsible for global influenza pandemics, while influenza B and C are responsible for epidemics of shorter duration. Global pandemics occurred in 1918, 1957, and 2009–2010 (the H1N1, swine flu pandemic), causing millions of deaths; the 1918 influenza A pandemic was responsible for approximately 40–50 million deaths [28].

In the USA, disease caused by influenza typically occurs seasonally, beginning in October, peaking between January and March, and subsiding in early May. In tropical climates, the influenza season may last throughout the year. The influenza virus spreads via large respiratory droplets, primarily through close contact, but the virus can also survive on fomites. The incubation period is 2 days, with a range of 1–4 days. Adults are infectious from 1 day prior to symptom onset through 5–10 days after symptoms begin. Children and immunocompromised hosts have a more prolonged period of continued viral shedding and infectivity. Uncomplicated influenza illness symptoms include abrupt onset of fever, malaise, myalgias, cough, pharyngitis and headache and are typically self-limited, lasting 7–10 days. Presentation may be atypical in children and the elderly. A common complication of influenza

infections includes secondary bacterial infections, particularly *Staphylococcus aureus*, *Streptococcus pneumoniae* (*S. pneumoniae*), and *Streptococcus pyogenes.* Other rarer complications include myocarditis, rhabdomyolysis, encephalitis, delirium, and other neuropsychiatric adverse events. In pregnancy, infection can lead to preterm delivery, small-for-gestational-age infants, and fetal death, in addition to maternal complications. Infants, the elderly, and people with chronic conditions are at high risk of influenza-related morbidity and mortality [10].

Influenza Vaccine and Vaccine Efficacy

The first influenza vaccine was approved for military use in the USA in 1945 and civilian use in 1946 [29]. ACIP recommends influenza vaccines for all persons aged 6 months and older. Children under 8 require two doses of influenza vaccine if getting vaccinated for the first time. There are several types of influenza vaccines available. Most are injectable vaccines designed to be injected into the muscle with a needle. There are also injectable vaccines given via a jet injector and intradermal and nasal vaccines. Influenza vaccines are either trivalent (includes two strains of influenza A and one strain influenza B) or quadrivalent (includes two influenza A strains and two influenza B strains). Some vaccines come with adjuvants, and there is one recombinant vaccine that is egg-free. Trivalent vaccines are made to protect against three flu viruses: influenza A H1N1 virus, influenza A H3N2 virus, and one influenza B virus. Quadrivalent vaccines are made to protect against four viruses which include the three viruses found in the trivalent vaccine plus a second influenza B virus [30].

Injectable influenza vaccines include those that are trivalent inactivated vaccines:

- Standard trivalent vaccine for different ages (IIV)
  - One formulation given with a jet injector instead of a needle (for those 18–54)
- High-dose trivalent vaccine (for those 65 and older)
- Recombinant trivalent vaccines (egg-free for those over 18)
- Trivalent made with adjuvant (for those 65 and older)

Injectable influenza vaccines include those that are quadrivalent inactivated vaccines (IIV4):

- Standard quadrivalent vaccine (for different ages)
- An intradermal quadrivalent vaccine (for those 18–64) injected into the skin, not muscle
- Quadrivalent vaccine containing virus grown in cell culture, new 2016 (for those over 4 years)

The quadrivalent nasal spray live attenuated influenza vaccine (LAIV) (for those 2–49 years of age) has been recommended during some flu seasons, but not all.

The influenza vaccine is unique in that it is the only vaccine reformulated annually to confer protection for different viruses each flu season July 1–June 30. Exposure to influenza one season does not confer antibody protection to influenza the following year. In addition to viral changes through antigenic drift and antigenic shift, host factors such as age, medical conditions, prior infections, and prior vaccinations can affect how beneficial the vaccine is to the host [31]. Vaccine effectiveness is measured via the Influenza Vaccine Effectiveness Network, a collaboration among institutions in five geographic locations. Observational studies compare the frequency of influenza illness among vaccinated and unvaccinated people. Patients with respiratory symptoms are tested for influenza, influenza vaccination status is recorded, and vaccine effectiveness is calculated [31]. Influenza vaccine has demonstrated varying degrees of effectiveness year to year. Effectiveness has ranged from 10% to 60% from 2005 through 2016 [32] (Table 4.2).

Table 4.2 Adjusted vaccine effectiveness estimates for influenza seasons from 2005 to 2016

Influenza season[†]	Reference	Study site(s)	No. of patients[‡]	Adjusted overall VE (%)	95% CI
2004–05	[209]	WI	762	10	−36, 40
2005–06	[209]	WI	346	21	−52, 59
2006–07	[209]	WI	871	52	22,70
2007–08	[210]	WI	1914	37	22, 49
2008–09	Unpublished	WI, MI, NY, TN	6713	41	30, 50
2009–10	[212]	WI, MI, NY, TN	6757	56	23, 75
2010–11	[215]	WI, MI, NY, TN	4757	60	53, 66
2011–12	[214]	WI, MI, PA, TX, WA	4771	47	36, 56
2012–13	[213]	WI, MI, PA, TX, WA	6452	49	43, 55
2013–14	[346]	WI, MI, PA, TX, WA	5999	52	44, 59
2014–15	[347]	WI, MI, PA, TX, WA	9311	19	10, 27
2015–16[a]	ACIP presentation, Flannery [332 kB, 26 pages] [211]	WI, MI, PA, TX, WA	7563	47[a]	39, 53[a]

[a]Estimate from Nov 2, 2015–Apr 15, 2016. http://www.cdc.gov/flu/professionals/vaccination/effectiveness-studies.htm

A high-dose, trivalent, inactivated influenza vaccine was created to improve antibody responses in adults aged 65 and older. Vaccine efficacy studies show that when compared to the standard-dose vaccine, the high-dose vaccine was 24.2% more efficacious than the standard-dose vaccine by inducing a significantly higher antibody response and better protection against laboratory-confirmed influenza [33]. Additional evaluation of this data showed that even when stratifying the efficacy by age, comorbidities, frailty, and the number of conditions, the high-dose vaccine was consistently more efficacious than the standard-dose vaccine irrespective of age and presence/number of comorbid or frailty conditions [34].

Recent studies do not show increased efficacy of the live attenuated influenza vaccine to the inactivated influenza vaccine. No consistent conclusions have been found regarding the use of the live, attenuated influenza vaccine from year to the next [31]. Over the past several years, recommendations to preferentially give the live attenuated vaccine over the killed vaccine to children have been made and retracted, and during the 2016–2017 flu season, no recommendation was made to give live attenuated influenza vaccine.

Polio

Poliomyelitis is a crippling and potentially fatal viral disease caused by three serotypes of the species enterovirus C, of the *Picornaviridae* family. Polio spreads from person to person via the oral-oral or fecal-oral route and replicates in the oral and intestinal mucosa. It has no cure and vaccination is the best protection from the disease. Polio was once considered one of the most feared diseases in the USA: in the early 1950s, polio outbreaks caused more than 15,000 cases of paralysis each year in the USA. After the introduction of the trivalent inactivated poliovirus vaccine (IPV) in 1955 and the trivalent oral poliovirus vaccine (OPV) in 1963, the number of polio cases fell rapidly to less than 100 in the 1960s and fewer than 10 in the 1970s. Since 1979, no cases of polio have originated in the USA, but polio disease has been brought into the country by travelers infected with polio [35].

Most polio disease is asymptomatic: approximately 72 out of 100 infected persons do not have any visible symptoms. The incubation period for the onset of initial symptoms is between 3 and 6 days. Approximately 24% of infected patients experience fever, malaise, nausea and vomiting, sore throat, and headache. Minor illness progresses to severe headache and neck stiffness, typically lasting 2–10 days, and completely resolves. Those that develop more serious symptoms affecting the brain and spinal cord may experience paresthesias, meningitis, and paralysis. Less than 1% of cases of poliomyelitis progress to paralytic polio: when cases do progress, the initial typical mild symptoms appear to resolve before flaccid paralysis rapidly develops. Paralysis can continue to extend for several days, affecting proximal more than distal muscles. In 5–10% of cases of paralytic polio, the respiratory muscles are affected, leading to respiratory insufficiency and death. Some survivors of paralytic polio recover with permanent paralysis, muscle atrophy, and/or skeletal defor-

mities. A noninfectious post-polio syndrome can occur 15–40 years following infection and results in irreversible muscle weakness [35].

Since 1988, the World Health Assembly has been working toward complete eradication of poliovirus from the globe. Recently, worldwide surveillance detected type 1 poliovirus in three countries: Nigeria, Afghanistan, and Pakistan [36]. Until the world is rid of polio, vaccination efforts must continue.

Polio Vaccine and Vaccine Efficacy

The first polio vaccine was created by Dr. Jonas Salk and licensed in 1955. It is an inactivated vaccine, given as an injection, and prevents three strains of polio. The second (live attenuated) polio vaccine licensed for use in the USA was created by Dr. Albert Sabin. It also prevents three strains of polio and is given as an oral vaccine. The Sabin oral poliovirus vaccine (OPV) was given in the USA from 1963 through 2000. Today in the USA, only the Salk inactivated vaccine (IPV) is given, as a four-dose series at 2, 4, and 6–18 months of age and a booster dose at 4–6 years of age. Adult travelers to polio-endemic or high-risk areas of the world are recommended to get a polio booster vaccine. Those persons working in a laboratory and handling specimens that might contain polioviruses and healthcare workers treating patients who could have polio should also be vaccinated. In 1988, study investigators demonstrated at least 99% detectable antibodies to all three types of wild virus following the second dose of the polio vaccine and 99–100% detectable antibody levels after the third dose of IPV [37].

Measles

Measles, also known as morbilli or rubeola, is caused by a single-stranded, enveloped RNA virus with one serotype. Humans are the only natural hosts. Measles is spread by respiratory droplets directly or via aerosolized virus and is one of the most infectious diseases known to man, with 12–18 secondary cases following a single infection. In the decade before the live measles vaccine was licensed in 1963, an average of 549,000 measles cases and 495 measles deaths were reported annually in the USA. As most cases were not reported, it is more likely that an average of 3–4 million people were infected with measles annually during the 1950s. In 2000, measles was declared eliminated from the USA (defined by the absence of endemic measles virus transmission for 12 months or longer). However, measles cases and outbreaks still occur every year in the USA with imported cases of disease affecting susceptible Americans [38]. Healthcare providers should report suspected measles cases to their local health department within 24 h.

Outbreaks of measles virus in temperate regions typically occur in late winter and early spring with epidemics occurring every 2–5 years. Worldwide, prior to

routine vaccination, an estimated 130 million cases and 70 million deaths occurred annually secondary to measles. Today, in developed countries, the death rate is less than 0.5% but is nearer 10% in areas with limited healthcare resources. Measles is still endemic in many countries. Of the estimated 20 million people who become infected with measles annually worldwide, over 130,000 people die [38].

The incubation period for measles lasts up to 14 days. After the incubation period, symptoms of fever and the "three C's" (cough, coryza, and conjunctivitis) develop. Pathognomonic small, blue-white lesions of the buccal mucosa known as Koplik's spots appear prior to the onset of rash. The characteristic erythematous, maculopapular rash presents initially on the face and ears and then spreads centrifugally to the trunk and extremities, lasting 3–5 days before becoming confluent prior to resolution. Desquamation may occur. Up to 40% of affected people suffer complications, including diarrhea, secondary viral or bacterial pneumonias, stomatitis, croup, otitis media, keratoconjunctivitis leading to blindness, encephalitis, and death. Infection during pregnancy can lead to severe maternal infection including risk of death, preterm labor, and fetal demise. Subacute sclerosing panencephalitis may present 5–15 years after acute infection in up to 1 in 10,000–100,000 cases, leading to cognitive and motor dysfunction, seizures, and death [10, 39]. Measles can be prevented with measles-containing vaccine administered as the combination measles-mumps-rubella (MMR) vaccine. Vaccination levels of greater than 95% are required to prevent and contain disease outbreaks [39, 40].

Mumps

Mumps, caused by the mumps virus, was once a common childhood condition that is typically self-limited and relatively benign. It is moderately contagious and is spread to the upper respiratory tract through respiratory droplets, direct contact, or fomites and has an incubation period of 15–24 days. Mumps is characterized by unilateral or bilateral non-purulent parotid gland swelling, present in 60–75% of cases. The parotid gland swelling typically occurs after the prodromal phase, characterized by fever, anorexia, malaise, and headache. Central nervous system involvement is common, with over 50% of cases demonstrating elevated white blood cell counts in the cerebrospinal fluid. Between 1 and 10% of patients develop meningitis, which is universally benign and without long-term sequelae. Orchitis is common in postpubertal males with the rare complication of infertility. In pregnancy, especially during the first trimester, spontaneous abortions may occur. Other less common complications of mumps include encephalitis, chronic sensorineural hearing loss, mastitis, pancreatitis, EKG abnormalities, and joint involvement. Prior to routine vaccination, nearly all people were infected with mumps by adolescence, with peak incidences occurring in winter and spring. Vaccination has reduced rates of infection in the USA by 99%. Today, incidences have been reported around 300 per 100,000 annually, but underreporting of infection is suspected. Recent outbreaks have occurred in populations with routine mumps vaccination. Outbreaks are

suspected to be secondary to insufficient immunization to reach herd immunity threshold as well as waning immunity of MMR vaccination. Outbreaks typically involve adolescents and adults, who experience higher levels of complications than children [10, 41].

Rubella

Rubella, or German measles, and congenital rubella syndrome (CRS) are caused by the rubella virus, an enveloped, positive-stranded RNA virus classified as a *Rubivirus* in the *Togaviridae* family [42]. There is no treatment to cure rubella. Outbreaks usually occur in the spring, while epidemics occur in cycles ranging from 3 to 9 years. Before the rubella vaccine was licensed in the USA in 1969, rubella was a common disease, occurring primarily among young children. Rubella incidence has decreased by more than 99% from the pre-vaccine era and was deemed eliminated from the USA in 2004 [42].

Rubella is spread via the respiratory route and is moderately contagious. Humans are the only natural hosts. Disease is typically benign and self-limited and most prevalent in children and young adults. Symptoms include a generalized erythematous, maculopapular rash, mild fever, and lymphadenopathy. The average incubation period of rubella virus is 17 days with a range of 12–23 days. People infected with rubella are most contagious when the rash is erupting, but can be contagious from 7 days prior to rash development and up to 7 days after rash development [42]. Rubella complications include arthritis, encephalitis, and thrombocytopenia. CRS is a devastating illness affecting infants exposed to rubella in utero. Maternal viremia leads to placental and fetal infection, and spontaneous abortion may result early in the pregnancy. Clinical sequelae in surviving infants include encephalitis, microcephaly and mental retardation, autism, cochlear deafness, cataracts, and cardiac conditions. Neonates may have characteristic "blueberry muffin" lesions as a result of dermal erythropoiesis, interstitial pneumonitis, and hepatosplenomegaly. Following widespread vaccination in the Americas and Europe, current data suggests less than two cases of CRS per 100,000 live births. Unfortunately, rubella and CRS remain endemic in many areas of the world, with the annual global incidence of CRS of greater than 100,000 [43].

MMR Vaccine and Vaccine Efficacy

The measles, mumps, rubella vaccine (MMR, M-M-R® II,) was licensed in 1971 as a live combination vaccine against measles, mumps, and rubella viruses [52]. Today, the vaccine contains a more attenuated measles virus from Enders' attenuated Edmonston strain [53]. Current ACIP recommendation is a two-dose series MMR for children at 12–15 months of age and at 4–6 years of age (may be given earlier,

if at least 28 days after the first dose). Some infants traveling out of the country should get a dose of MMR before 12 months of age, and this dose will not count toward their routine series. Adults born before 1957 are generally considered immune to measles, mumps, and rubella and do need the MMR vaccine. Adults born after 1956 who were never vaccinated, and who never had the three disease, are recommended to get the MMR vaccine. Children between 1 and 12 years of age can get a combination quadrivalent measles, mumps, rubella, and varicella vaccine (MMRV, ProQuad®).

Vaccine effectiveness in the prevention of measles after one dose of MMR vaccine in recipients greater than 1 year of age, ranged from 87% to 97% in studies conducted in the USA from 1972 to 1986 [44]. In 1989, ACIP recommended that the routine vaccination schedule be increased from a one-dose to a two-dose schedule after major measles outbreaks occurred in the previous years (including outbreaks in schools with greater than 98% vaccination rates) [45]. Vaccine effectiveness from a 1994 outbreak at an elementary school was approximated at 92% in those children having received one dose of MMR and 100% in those with two doses [46]. Increased effectiveness of patients receiving two doses versus only one dose has been subsequently proven in other outbreaks [47, 48], and the two-dose MMR series has been shown to maintain protection from measles for up to 10 years after the second dose of MMR [49].

The first single live mumps virus vaccine, Mumpsvax®, containing mumps virus from the Jeryl Lynn™ (B level) strain, was licensed in the USA in 1967. This is still the same viral strain used in the current MMR vaccine [13, 50]. Vaccine efficacy against mumps, based on antibody titers, was 95.6% in 5 months after vaccination [51]. Post initiation of MMR vaccine, incidence of mumps rapidly declined in the USA by 98%, from 152,209 cases in 1968 to 2982 cases in 1985 [52]. Clinical efficacy reported from 1985 to 1988 varied from 70 to 91% during the one-dose MMR era [53–55]. After the ACIP recommendation to increase MMR vaccination to a two-dose series, vaccine effectiveness was calculated using data from a 2005 mumps outbreak: vaccine efficacy was 91.6% for those individuals with two doses of MMR (53%) compared to 79.7% with one dose (32%) [56]. Another study using data from a 2006 mumps outbreak determined vaccine effectiveness to be 76–88% for those with two doses of MMR when compared to those with one dose. Of those individuals who had received a two-dose vaccination series, but still contracted mumps, 74–79% of them had received their second dose greater than 10 years prior [57]. Thus the potential benefit of a third dose of MMR during an outbreak has been investigated: a 75.6% reduction in mumps attack rate was seen in those subjects that received a third dose [58]. It remains to be seen whether mumps booster recommendations will change.

The first single, live rubella virus vaccine, Meruvax® II, containing the Wistar RA 27/3 rubella strain, was licensed in the USA in 1979 and is the same viral strain used in the current MMR vaccine [13, 59]. Vaccine efficacy with monovalent rubella vaccine after one dose of the 27/3 strain was historically high, at greater than 95% [60]. The duration of protection from the 27/3 strain, defined by presence of antibodies, was detected at decreasing levels up to 16 years after vaccination. [61]

WHO cites development of rubella antibodies in 95–100% of susceptible persons aged ≥12 months after a single dose of the MMR vaccine, and in outbreak situations, the effectiveness of different rubella vaccines has been estimated at 90–100% [62].

Hepatitis B

Hepatitis B virus (HBV) causes hepatitis B liver infection, the most common viral infection worldwide. There are an estimated 2 billion people infected with HBV and 350 million chronic carriers of HBV worldwide. Over 500,000 people die each year of hepatitis B or its complications [63]. In the USA, 850,000–2.2 million persons are estimated to be living with HBV infection. HBV is transmitted through percutaneous or mucosal exposure to blood or body fluids of an infected person, such as from an infected mother to her newborn during childbirth, through close personal contact within households, through unscreened blood transfusions or unsafe injections in healthcare settings, through injection drug use, and from sexual contact with an infected person. Adults with diabetes are at an increased risk of acquiring HBV infection if they share diabetes-care equipment such as blood glucose meters, finger-stick devices, syringes, and/or insulin pens [64].

In acute HBV infection, nearly all children and up to 70% of adults are asymptomatic. Some acute infections lead to chronic infections and long-term complications. The risk of progression to chronic HBV infection is inversely proportional to age of disease acquisition. While more than 90% of vertically transmitted perinatal infections lead to a chronic carriage state, more than 90% of infections in adolescence or adulthood resolve spontaneously. Chronic HBV infection may lead to hepatocellular hepatic cirrhosis or hepatocellular carcinoma (HCC). Nearly 25% of people infected in childhood will progress to develop cirrhosis or HCC [10]. Half of the total cases and nearly all childhood cases of HCC are related to chronic HBV infection [65, 66]. Vaccination against HBV has been successful in reducing infection with HBV and its complications, including a significant decline in HCC [67].

When present, symptoms of hepatitis B include anorexia, nausea and vomiting, abdominal pain, malaise, and jaundice, lasting for days to weeks. These may not appear for up to 6 months after the time of infection. Extrahepatic manifestations include arthralgias, macular rashes, and glomerulonephritis. More rarely, fulminant hepatitis may occur with rapidly progressive symptoms and death without immediate interventions.

Unvaccinated adults account for 95% of new HBV infection. Persistent attention to vaccination status of adults, especially those with high-risk behaviors, should remain as an area of focus among healthcare professionals [68, 69]. With the initiation of universal childhood hepatitis B (HepB) vaccination starting in 1991, rates of acute hepatitis B in vaccinated children and adolescents decreased by 94%. Furthermore, infant HepB vaccination decreases perinatal transmission in infants born to HBV-infected mothers. Combined administration of HepB vaccine and

hepatitis B immunoglobulin within 12 h of birth provides 94% efficacy in preventing vertical transmission in infants born to HBV-infected mothers. Administration of the complete HepB vaccination series along with immunoglobulin is vital for these infants, as the infection rate is 6.7% among infants with less than three doses of vaccine compared to 1.1% in those with complete series [70].

Hepatitis B Vaccine and Vaccine Efficacy

HepB vaccination is given as three or four doses over a 6-month period and is recommended for:

- All infants, starting with the first dose within 24 h of birth, series completed by 6–18 months of age
- All children and adolescents younger than 19 years old not already vaccinated
- People whose sex partners have hepatitis B
- Sexually active persons not in a long-term, mutually monogamous relationship
- Persons seeking evaluation or treatment of a sexually transmitted disease
- Men who have sex with men
- People who share needles, syringes, or other drug injection equipment
- People in close household contact with someone infected with HBV
- Healthcare workers and public safety workers at risk for exposure to body fluids
- People with end-stage renal disease
- Residents and staff of facilities for the developmentally disabled
- Travelers to regions with moderate or high rates of HBV infection
- People with chronic liver disease or chronic kidney disease
- People with HIV
- People with diabetes ages 19–59, consider for those over 60
- Persons in correctional facilities
- Anyone who wishes to be protected from hepatitis B

The first vaccine to protect against hepatitis B was human plasma derived and licensed in 1981 [71]. However, it was later discontinued due to public concern for potential HIV transmission despite studies verifying the safety of the vaccine and no documented cases of HIV transmission [72]. Recombivax HB® was licensed in 1986 as a genetically engineered recombinant vaccine to satisfy the fears of potential disease transfer from plasma-derived vaccines. A few years later, Engerix-B® was licensed in 1989 for the prevention of infection by all subtypes of HBV [1, 73, 74]. Either recombinant vaccine conveys a 95–100% seroprotective rate in vaccinated children [75]. A three-dose vaccination series is recommended, and efficacy is not altered if vaccine brands are interchanged during the series [76]. A 2009 study found that 60% of individuals had sufficient immunity 22 years after the primary vaccine series [77]. Booster doses after the primary series completion are not currently recommended. Combined hepatitis A (HepA) and HepB vaccines indicate

Table 4.3 Available hepatitis B vaccines

Vaccine contents/ abbreviation	Trade name	Year licensed	FDA-approved age indication	Volume of dose (mL)	Dose series
HepB	Engerix-B®[a]	1989	Birth through 19 years	0.5	3 doses: at 0, 1, and 6 months of age
			20 years and older	1	3 doses: at 0, 1, and 6 months of age
HepB	Recombivax HB®[b]	1983	Birth through 19 years	0.5	3 doses: at 0, 1, and 6 months of age
			11 years through 15 years		3 doses: at 0, 1, and 6 months of age
			11 years through 15 years	1	2 doses: at 0, 4–6 months
			20 years and older		3 doses: at 0, 1, and 6 months of age
HepA + HepB	Twinrix®[c]	2001	18 years and older	1	3 doses (standard): at 0, 1, and 6 months of age
					4 doses (accelerated): at 0, 7, and 21–30 days, followed by a booster dose at month 12
DTaP + HepB + IPV	Pediarix®[d]	2002	6 weeks through 6 years	0.5	3 doses: at 2, 4, and 6 months of age

[a]Engerix-B [Package Insert] [1]
[b]RECOMBIVAX HD [Package Insert] [73]
[c]TWINRIX [Package Insert]. [Internet] [110]
[d]Pediarix [Package Inset] [Internet] [317]

similar rates of immune response to both anti-HAV and anti-HBV when compared to monovalent vaccines [78].

The following vaccines are available to protect against hepatitis B (Table 4.3):

- Recombivax HB®, licensed in 1983, and Engerix-B®, licensed in 1989, are recombinant HepB vaccines given as three-dose series, at birth, 1–2 months, and 6–18 months of age.
- Twinrix® is a combined HepA (inactivated) and HepB (recombinant) vaccine licensed in 2001 for persons 18 years and older against disease caused by HAV and HBV given as a three-dose series at 0, 1, and 6 months of age.
- Pediarix® (DTap-IPV-HepB) licensed in 2002 is a combined diphtheria and tetanus toxoids and acellular pertussis adsorbed, recombinant hepatitis B, and inactivated poliovirus vaccine given as a three-dose series at 2, 4, and 6 months of age.

Haemophilus influenzae

Haemophilus influenzae is a type of bacteria that mainly causes illness in infants and young children, and is the leading cause of a variety of invasive infections in children. There are six identifiable types of *H. influenzae* bacteria (a through f) and other non-identifiable (nontypeable) types [79]. Much invasive *H. influenzae* disease is caused by the encapsulated type b serotype (Hib), which can cause ear infections, meningitis, epiglottitis, cellulitis, septic arthritis, pneumonia, and bacteremia. Between 3% and 6% of Hib cases in children are fatal; up to 20% of patients who survive Hib meningitis have permanent hearing loss or other long-term neurological sequelae. Patients 65 years of age and older with invasive Hib disease have higher case fatality ratios than children and young adults [79].

Prior to introduction of Hib vaccination, Hib was a frequent nasopharyngeal colonizer in infants and preschool children, serving as a reservoir for transmission of the disease among children and their daycare or household contacts. Incidence of invasive disease was greater than 300 per 100,000 children, with most invasive disease occurring in children under the age of 5. Today, there are fewer than 1 case per 100,000 children under age 5 in the USA [89, 90].

Haemophilus influenzae *Vaccine and Vaccine Efficacy*

The introduction of conjugate vaccines against Hib in 1988 resulted in a rapid decline of disease over a brief period compared to other vaccines [80]. Several brands of Hib vaccine are available, and depending on which vaccine is used, a child is recommended to receive either three or four doses at 2, 4, and 6 months of age (6-month dose may not be necessary depending on brand of vaccine) and a booster dose at 12–15 months of age. Healthy adults and children over 5 years of age are not recommended to receive the Hib vaccine. However, it is recommended for children and adults with special conditions such as asplenia or sickle cell disease, presurgical splenectomy, following a bone marrow transplant, or for those with HIV.

There are currently three monovalent Hib vaccines available in the USA, differing by the protein conjugate. PedvaxHIB® was the first of the currently available vaccines approved in 1989 and is conjugated to an outer membrane protein complex of the B11 strain of *Neisseria meningitidis* serogroup B [81]. ActHIB® and Hiberix® were approved in 1993 and 2009, respectively, and are conjugated to tetanus toxoid [82, 83]. The antibody response after three doses of PedvaxHIB® or ActHIB® is similar, 88% and 97%, respectively [84]. Hiberix® was initially approved as a booster dose in the Hib series (prior to fifth birthday), after completion of the primary series [85]. Immunogenicity of Hiberix® was established via a noninferiority study, meeting minimal protective antibody levels [83]. The incidence of *Haemophilus influenzae* invasive disease in children under 5 years old decreased by 97% during the decade of 1987–1997 [86].

Varicella Zoster Virus: Chicken Pox

Varicella zoster virus (VZV) is the human herpesvirus responsible for causing the highly contagious disease varicella (chicken pox), as well as herpes zoster (shingles). Varicella results after primary infection with VZV, which then stays in the body in the sensory nerve ganglia as a latent infection. Reactivation of latent infection causes herpes zoster. The incubation period for varicella is 14–16 days after exposure to varicella or a herpes zoster rash, with a range of 10–21 days [87]. VZV is spread primarily through the respiratory route, but can also be contracted through direct contact with skin lesions, or across a mother's placenta. The rash of varicella is generalized and present in varying stages of development progressing from macules to papules to vesicles before crusting. The rash usually appears first on the head, chest, and back and then spreads to the rest of the body. Infection is generally benign and self-limiting. Serious complications include bacterial superinfection, cellulitis, pneumonitis, meningoencephalitis, and stroke. Severe complications are more common when primary infection occurs in adulthood. Congenital varicella syndrome (CVS) is a rare disorder that affects infants born to mothers infected with varicella during the first 20 weeks of pregnancy. Newborns may show skin lesions, limb abnormalities, chorioretinitis, microcephaly, and cognitive impairment. If CVS develops within the final days before delivery, or within a day or two afterward, there is a risk of neonatal varicella, which carries a mortality rate as high as 30% [10, 88].

Prior to the availability of VZV vaccination, mortality rates secondary to varicella infection were 0.41 per 100,000 in the USA, with a hospitalization rate of 2.7 per 100,000. Vaccination has significantly decreased those rates to 0.14 and 0.6, respectively [89]. Additionally, varicella outbreaks confer high financial costs to society with vaccination saving money. Compared to no vaccination program, the US varicella vaccination program results in societal cost savings of over $0.9 billion dollars [90].

Varicella Zoster: Chicken Pox Vaccine and Vaccine Efficacy

Varivax® was licensed in 1995 initially as a single dose, live attenuated varicella virus vaccine [91]. Children who have never had chicken pox are recommended to get two doses of varicella vaccine at 12–15 months of age and again at 4–6 years of age (may be given earlier, if at least 3 months after the first dose). People 13 years of age and older who have never had chicken pox or received the vaccine are recommended to get two doses at least 28 days apart. Varivax® demonstrated 100% efficacy 9 months postvaccination, in healthy naïve recipients aged 1–14 years [92]. Long-term efficacy was demonstrated to be 96% after a second varicella season and 95.1% after 7 years [93]. Since routine varicella vaccination started in the USA, several post licensure efficacy studies have demonstrated varied efficacy. Vaccine effectiveness after one dose varies depending on categorization of varicella severity and

clinical or lab diagnosis [94]. A 2004 study reported vaccine efficacy of 97% one year postvaccination, declining to 86% after two years and 81% after eight years [95]. In June 2007, ACIP recommended a second varicella dose between ages 4 and 6 years [96]. Efficacy following two doses of varicella was calculated at 98.3% compared to 86% following one dose of varicella in children 4 years and older [97]. Unfortunately, despite improved vaccine efficacy after two doses, outbreaks are still reported, but with less impact. The impact of the two-dose varicella vaccination program has resulted in a 60% reduction in outpatient visits and a 38% reduction in hospitalizations [98]. MMRV (ProQuad® licensed in 2005), a combination vaccine containing both varicella and MMR vaccines, may be given to persons 12 years of age and younger. MMRV was found to be noninferior to MMR® II and Varivax® [99].

Hepatitis A

The *Hepatitis A virus* (HAV) causes hepatitis A liver infection, an acute, usually self-limited viral illness in children, but a potentially more serious infection in adults. In children under age 6, infection with HAV is usually asymptomatic or produces mild symptoms. Adults may experience more severe symptoms that include fever, malaise, nausea, vomiting, abdominal pain, jaundice, and, rarely, acute fulminant hepatitis. The risk of jaundice and other severe symptoms increases with age. Up to 10% of infected patients may have a relapsing course lasting up to 6 months. Unlike infections with hepatitis B and C, HAV infection does not lead to chronic liver infections. Worldwide, HAV is responsible for over 1 million cases of acute hepatitis annually, leading to 35,000 deaths [10, 100, 101]. In the USA, the number of Hepatitis A cases reported has declined from 1670 reported cases in 2010 to 1239 reported cases in 2014 [102].

HAV is transmitted through the fecal-oral route, through close person-to-person transmission, and during foodborne outbreaks. The average incubation period for hepatitis A is 28 days (range 15–50 days) [103]. In 1996, ACIP recommended HepA vaccination only to those persons at high risk for the disease, but by 1999, the recommendations were expanded to include children living in 11 states with average hepatitis A rates of over 20 cases per 100,000 population. In 2006, ACIP recommendations again expanded to include routine vaccination of all children at 1 year of age and older in all 50 states.

Hepatitis A Vaccine and Vaccine Efficacy

Hep A inactivated vaccine is given as a two-dose series given over 6 months for children and adults. A combined HepA and HepB vaccine is available for adults 18 years of age and older, given in a three-dose series over 6 months. HepA vaccination is recommended for:

- All children aged 12 months or older
- Travelers to certain countries
- Family members or caregivers of a recent adoptee from countries where hepatitis A is common
- Men who have sex with men
- Users of injection and non-injection illegal drugs
- People with chronic liver disease
- People treated with clotting factor concentrates
- People who work with HAV-infected animals or in a HAV research lab

There are currently three vaccines available to immunize against hepatitis A: two inactivated monovalent vaccines and one combination vaccine (Table 4.4).

Havrix® was licensed in 1995 initially for persons 2–18 years of age, and Vaqta® was licensed in 1996 for persons 2–17 years of age for prevention of disease caused by HAV [104, 105]. The two inactivated monovalent HepA vaccines were compared in an open-label randomized trial. They were shown to be similar in rapid serial conversion rates after the primary dose as well as demonstrating equivalent immunogenicity after one booster dose [106]. Two studies examining the vaccine efficacy over time found lasting antibody concentrations 17 years after primary vaccination series and seropositive protection rates greater than 95% after 25 years [107, 108]. Success of the HepA vaccine is illustrated by the 96.6% decrease in reported hepatitis A disease from 1996 to 2011 [109]. With recent increases in hepatitis A cases in adults over the age of 40, future vaccination efforts may need to focus on this older population [109].

Twinrix®, a combined HepA (inactivated) and HepB (recombinant) vaccine, was licensed in 2001 for persons 18 years of age and older against disease caused

Table 4.4 Available hepatitis A vaccines

Vaccine contents/abbreviation	Trade name	FDA-approved age indication	Volume of dose	Number of doses in series
HepA	Havrix®[a]	12 months through 18 years old	0.5 mL	Two
		19 years and older	1 mL	
HepA	Vaqta®[b]	12 months through 18 years old	0.5 mL	Two
		19 years and older	1 mL	
HepB + HepA	Twinrix® [c]	18 years and older	1 mL	Three

[a] Havrix [104]
[b]Vaqta [Package Insert] [105]
[c]TWINRIX [Package Insert]. [Internet] [110]

by HAV and HBV as a three-dose series at 0, 1, and 6 months [110]. Efficacy trials indicate similar rates of immune response to both anti-HAV and anti-HBV when compared to monovalent vaccines [111].

Rotavirus

Rotavirus is a contagious virus that causes acute, severe gastroenteritis and is the leading cause of gastroenteritis in infants and children worldwide. Rotavirus infects the proximal small intestine, producing an enterotoxin that destroys the epithelial surface, resulting in blunted villi, extensive damage, and shedding of massive quantities of virus in the stool. Spread is common within families [112]. Nearly every US child who is not vaccinated against rotavirus as an infant is expected to be infected with rotavirus within the first year of life. In developing countries, rotavirus gastroenteritis is responsible for approximately half a million deaths per year among children less than 5 years of age [113]. During the 1990s and early 2000s, rotavirus resulted in approximately 410,000 physician visits, 205,000–272,000 emergency department visits, and 55,000–70,000 hospitalizations among US infants and children, with total annual direct and indirect costs of approximately $1 billion [112].

Rotavirus is spread through the fecal-oral route, through person-to-person contact, and through fomites [114]. Risk factors associated with increased risk for hospitalization for infants include lack of breastfeeding, low birth weight, daycare attendance, the presence of another child less than 24 months of age in the household, and either having Medicaid insurance or having no medical insurance [115]. The incubation period for rotavirus gastroenteritis is 1–3 days. Reinfection occurs up to five times in the first 2 years of life, but severity of disease decreases with each subsequent infection. Peak incidence of infection occurs at 4–23 months of age. Symptoms include vomiting, followed by profuse and watery diarrhea that may lead to dehydration and electrolyte disturbances. Neurologic symptoms include encephalopathy, encephalitis, or seizures. Without supportive medical treatment, rotavirus can be deadly in children [116].

Since initiating regular vaccination, the USA has seen reductions in rotavirus activity ranging from 50 to 90%. Hospitalizations due to rotavirus acute gastroenteritis have declined by 50–90%, with all-cause acute gastroenteritis hospitalizations decreasing by 30–60% [117].

Rotavirus Vaccine and Vaccine Efficacy

Two rotavirus vaccines currently licensed for use in infants in the USA are recommended for either a two- or three-dose series between the ages of 2 months and 6 months, depending on the brand. Both vaccines are given orally, and the first dose of

either vaccine is most effective if given before a infant is 15 weeks of age. All infants should receive all doses of rotavirus vaccine before they turn 8 months old [118].

In 2006, RotaTeq® (RV5) was licensed as a pentavalent, oral, live three-dose vaccine series, and in 2008, Rotarix® (RV1) was licensed as a monovalent, oral, live two-dose vaccine series against rotavirus [13, 119]. The Rotavirus Efficacy and Safety Trial (REST) demonstrated RV5 had 98% efficacy against severe rotavirus gastroenteritis in the first season after immunization and sustained efficacy at 88% after the second rotavirus season, lasting for 3.1 years after the last vaccine dose. An 86% decrease in clinic visits and a 95.8% reduction in hospitalizations due rotavirus gastroenteritis were also shown. An extension trial of REST determined sustained efficacy of RV5 up to 3.1 years after the last dose of vaccine [120, 121]. Another study, the human rotavirus study, revealed RV1 had 84.7% efficacy against severe rotavirus gastroenteritis within the first year of life and hospitalization was avoided in 84% of vaccine recipients [122]. Moreover, RV1 demonstrated 90.4% efficacy against severe episodes after the second consecutive rotavirus season [123]. In addition, it is estimated that the societal cost savings of the complete vaccine series of RotaTeq® and Rotarix® are nearly 60 million dollars [124].

Pneumococcal Infections

Streptococcus pneumoniae (*S. pneumoniae*), or pneumococcus, is a common bacterial cause of otitis media, sinusitis, community-acquired pneumonia, and septicemia. The World Health Organization (WHO) estimates that *S. pneumoniae* kills close to half a million children under 5 years of age worldwide every year, with most deaths occurring in developing countries. Children younger than 2 years old, adults 65 years or older, and adults 19–64 years old with certain medical conditions or risk factors are at increased risk for pneumococcal disease. In the USA, prior to 2000, pneumococcal disease caused more than 700 cases of meningitis, 13,000 cases of septicemia, 5 million ear infections, and 200 deaths in children under the age of 5. Since the advent of a pneumococcal vaccine in 2000, severe pneumococcal disease has fallen by 88% in children [125].

Transmission of pneumococcal bacteria is through direct contact with respiratory secretions like saliva or mucus [126]. Asymptomatic nasopharyngeal carriage of pneumococcal serotypes is common in infants and children, especially in those who attend daycares or are exposed to overcrowded living situations [127]. Adults living with children may also be asymptomatic carriers. Disease is usually episodic, however, person-to-person transmission can occur via respiratory droplets.

The more severe clinical syndromes of pneumococcal disease result in pneumonia, bacteremia, and meningitis. *S. pneumoniae* is the most common clinical presentation of pneumococcal disease among adults and is one of the most frequent causes of community-acquired pneumonia. CDC estimates that as many as 400,000 hospitalizations from pneumococcal pneumonia occur annually in the USA. Bacteremia occurs in up to 25–30% of patients with a case fatality rate of 5–7%, higher among the elderly. Symptoms of pneumococcal pneumonia include an abrupt onset of fever

and chills or rigors after a short incubation period of 1–3 days. Typically, there is only a single rigor without repeated shaking chills. Other complications of pneumococcal pneumonia include empyema, pericarditis, and respiratory failure. Children with pneumococcal pneumonia often show tachypnea, retractions, and other symptoms of respiratory distress [128].

Invasive pneumococcal disease can also present initially as bacteremia, sepsis, and meningitis, without pneumonia occurring first. Among children 2 years of age and younger, bacteremia without a known site of infection is the most common invasive clinical presentation of pneumococcal infection, accounting for approximately 70% of invasive disease in this age group [125]. More than 12,000 cases of pneumococcal bacteremia occur each year with an overall case fatality rate of about 20%, or as high as 60% among elderly patients. Patients with asplenia who develop bacteremia may experience a fulminant clinical course. Estimates of invasive pneumococcal disease are 15–30 per 100,000 people per year in developed countries [128].

Furthermore, pneumococci cause over 50% of all cases of bacterial meningitis in the USA with an estimated 3000–6000 cases occurring each year [128]. Meningitis presents classically with fever, headache, and nuchal rigidity and can rapidly progress to obtundation and death. Fatality rates in children are currently less than 10% with appropriate antibiotic therapy, however, long-term sequelae including sensorineural hearing loss, seizures, motor dysfunction, and cognitive impairment occur in 20–50% of survivors. In the USA, invasive disease incidence in children under 5 decreased from 95 per 100,000 to 22–25 per 100,000 between 1999 and 2002, and rates continue to decline [129].

Pneumococcal Vaccines and Their Efficacies

There are currently two types of pneumococcal vaccines: pneumococcal conjugate vaccine (PCV13 or Prevnar 13®) and pneumococcal polysaccharide vaccine (PPSV23 or Pneumovax®). There are age-based as well as disease-based recommendations for the vaccines. (See https://www.cdc.gov/vaccines/vpd/pneumo/hcp/recommendations.html for full dosing recommendations.)

PCV13 is a 13-valent protein conjugate vaccine recommended for all children under 5 years of age, all adults 65 years or older, and people 6 years or older with certain risk factors.

PCV13 vaccine is recommended for:

- Infants and children younger than 2 years old in four-dose series at 2, 4, 6, and 12–15 months.
- Children 2–5 years (to receive one dose) with the following medical conditions such as the following:
  - Sickle cell disease
  - A damaged spleen or no spleen
  - Cochlear implant(s)

  - Cerebrospinal fluid (CSF) leaks
  - HIV/AIDS or other immunocompromising diseases such as diabetes, cancer, or liver disease
  - Chronic heart or lung disease
  - Who take medications that affect the immune system such as chemotherapy or steroids

- Adults 19 years or older (to receive one dose) with conditions that weaken the immune system such as HIV infection, organ transplantation, leukemia, lymphoma, and severe kidney disease.
- Children 6–18 years of age (to receive one dose) with certain medical conditions such as sickle cell disease, HIV, other immunocompromising conditions, cochlear implant, or CSF leaks who have not previously received PCV13 regardless of whether they have previously received the PCV7 (Prevnar®) or the PPSV23 should receive one dose PCV13.
- Children who are unvaccinated or have not completed the PCV series should get the vaccine (the number of doses recommended and the intervals between them will depend on the child's age when vaccination begins).
- PCV13 may be given at the same time as other vaccines, but it should not be given with PPSV23 nor with the meningococcal conjugate vaccines.

PPSV23 is a 23-valent polysaccharide vaccine recommended for all adults who are ≥65 years of age and for people 2–64 years of age who are at high risk for pneumococcal disease.

PPSV23 vaccine is recommended for:

- All adults ≥65 years
- Anyone 2–64 years of age or has a long-term health problem such as heart disease, lung disease, sickle cell disease, diabetes, alcoholism, cirrhosis, CSF leaks, or cochlear implant
- Anyone 2–64 years of age who has a disease or condition that lowers the body's resistance to infection such as long-term steroids, certain cancer drugs, and radiation therapy
- Any adult 19–64 years of age who is a smoker or has asthma

The PCV13 vaccine replaced the previously recommended 7-valent Prevnar® vaccine in 2010 [130]. Five additional serotypes added to the 7-valent vaccine provide protection against 61% of invasive pneumococcal disease strains [131]. Four doses of PCV13 are recommended to elicit the greatest antibody response to the greatest number of serotypes [130]. A meta-analysis of pneumococcal vaccination in children less than 24 months demonstrated an efficacy of 63–74% against invasive pneumococcal disease, 29% against otitis media, and 6–7% against clinical pneumonia for all serotypes. Due to the high burden of disease, even a low vaccine efficacy for otitis media and clinical pneumonia can result in a great impact overall [132].

The pneumococcal polysaccharide vaccine (PPV23) contains 23 of the strains that account for 85–90% of invasive pneumococcal disease cases. In studying and evaluat-

ing many studies, it is difficult to assess the efficacy and effectiveness of PPV23 due to the low frequency of invasive infection, inaccuracy of diagnostic criteria for pneumococcal pneumonia, and poor study methodologies. CDC reports effectiveness in case-control studies ranging from 56–81% against invasive disease [133].

Meningococcal Infections

Neisseria meningitidis (*N. meningitidis*) is the bacterial pathogen responsible for meningococcal diseases, caused by six of its 12 serogroups: A, B, C, W, X, and Y. Rates of disease range from 0.6 to 34% and are highest in children younger than 1 year and in adolescents and young adults aged 16 through 23 years, especially those living in overcrowded conditions such as military barracks and college dormitories. Approximately 500,000 cases of meningococcal disease occur annually, with the majority in the winter and fall. Serogroups B, C, and Y cause most of the illness seen in the USA, and serogroup A causes disease in developing countries and in what is known as the "meningitis belt" of sub-Saharan Africa. Nearly all invasive *N. meningitidis* organisms are encapsulated by a polysaccharide capsule. Rates of meningococcal disease have been declining in the USA since the late 1990s [134].

Transmission of *N. meningitidis* occurs through respiratory droplets in close person-to-person contact and exchange of respiratory and throat secretions (saliva or spit). About one in ten people are asymptomatic carriers of *N. meningitidis* in their posterior nasopharynx. Without treatment, the case fatality rate of *Neisseria* bacterial meningitis can be as high as 70%, and one in five survivors may be left with permanent sequelae including hearing loss, developmental delay, neurologic disability, and limb amputation [135]. Clinically, after an incubation period of 1–10 days, meningococcal infections have an abrupt onset of nonspecific symptoms including fever, chills, and malaise which can lead to meningococcal meningitis (50% of cases) and septicemia or bacteremia (35–40% of cases). A macular, maculopapular, petechial, or purpuric rash is classically present with meningococcemia. Meningococcal disease is a reportable condition in all states, and state and local health departments will conduct investigations when disease is reported to ensure all close contacts are provided prophylaxis [134].

Meningococcal Vaccines and Vaccine Efficacies

Meningococcal vaccines help protect against all three serogroups of meningococcal disease seen most commonly in the USA: serogroups B, C, and Y. There are three kinds of vaccines available in the USA:

- Meningococcal conjugate vaccine (Menactra®, MenHibrix®, and Menveo®)
- Meningococcal polysaccharide vaccine (Menomune®)
- Serogroup B meningococcal vaccine (Bexsero® and Trumenba®)

All 11–12-year-olds should be vaccinated with a single dose of a quadrivalent meningococcal conjugate vaccine (Menactra® or Menveo®). A booster dose is recommended at age 16.

Teens and young adults (16–23 years of age) may also be vaccinated with a serogroup B meningococcal vaccine (Bexsero® or Trumenba®), preferably at 16–18 years of age. Two-three doses are needed depending on the brand. Preteens, teens, and young adults should be vaccinated with a serogroup B meningococcal vaccine if they are identified as being at increased risk of meningococcal disease with certain medical condition such as asplenia, having complement component deficiency, and being infected with HIV (Table 4.5).

Menomune® (MPSV4) was the first tetravalent (serogroups A, C, Y, W-135) polysaccharide vaccine licensed for use in 1981 [13]. The immunogenicity and clinical efficacy of MPSV4 among the four serogroups varies across ages. In adults, MPSV4 demonstrated seropositive conversion to serogroup A (95%), serogroup C (100%), and serogroup W-135 (93%) [136]. Serogroup C is poorly immunogenic in children under 18–24 months, while serogroup A component elicits a comparable adult-like response by 4–5 years [137].

Vaccine efficacy was demonstrated to be 85% in subjects 2–29 years [138]. Antibody response to serogroup A and C in children quickly declined to near levels of unimmunized children between booster doses up until 66 months of age [139]. In adults, protective antibody concentrations against serogroup A and C lasted for 10 years [140]. The poor immunogenicity and rapid decline of antibody response to MPSV4 led to the development of conjugated polysaccharide vaccines.

Menactra® was the first conjugate tetravalent (serogroups A, C, Y, W-135) polysaccharide vaccine approved in 2005 for use in ages 9 months to 55 years old [141]. Menactra® licensure was granted via demonstration of noninferior immunogenicity as compared to MPSV4 [137]. In subjects aged 2–10 and 11–18 years, the immunogenicity of Menactra® compared to MPSV4 was higher one month after the first vaccination and remained higher three years after primary vaccination [142, 143]. Conversely, in subjects aged 18–55 years, the percentage of subjects with protective antibody levels was higher in the MPSV4 group than the Menactra® group; however, noninferiority was still established [137].

Menveo®, a second conjugate tetravalent polysaccharide vaccine, was approved in 2010, initially for ages 11–55 years old [13]. For subjects aged 11–17 and 19–55, Menveo® had significantly greater antibody levels for all four serogroups compared to MPSV4 one month after vaccination, and higher levels were maintained 12 months after vaccination (exception serogroup A) [144]. Menveo® has also demonstrated to be noninferior to Menactra® across all four serogroups (notably statistically superior for groups C, W, and Y); thus, the age indication was expanded, ultimately to include those 2 months and older [13, 145]. The duration of protective antibody concentration has been demonstrated to be up to 5 years in the adolescent population. In 2010, ACIP recommended a meningococcal booster dose at age 16. More robust studies are needed to examine persistent efficacy after the adolescent

Table 4.5 All available vaccines

Vaccine	US trade name(s)	Infectious agent(s) covered	Vaccine type	Resources
Adenovirus type 4 and type 7	Adenovirus type 4 and type 7	Adenovirus	Live	[216]
Anthrax	BioThrax	*B. anthracis*	Inactivated	[217]
BCG	BCG Vaccine USP[a]	*M. tuberculosis*	Live	[218–222]
Cholera	VAXCHORA[b]	*V. cholerae*	Inactivated	[223, 224, 348]
Dengue	NA[c]	Dengue virus, serotypes 1–4	Live	[225]
Diphtheria and tetanus	Diphtheria and Tetanus Toxoids Adsorbed USP[d]	*C. diphtheriae, C. tetani*	Toxoid	[226–230]
Diphtheria, tetanus and pertussis (acellular)	DAPTACEL, INFANRIX	*C. diphtheriae, C. tetani, B. pertussis*	Toxoid, subunit	[14, 15]
Diphtheria, tetanus and pertussis (whole cell)	NA[e]	*C. diphtheriae, C. tetani, B. pertussis*	Toxoid, inactivated	[234, 235]
Diphtheria, tetanus, pertussis (acellular), hepatitis B and poliovirus	Pediarix	*C. diphteriae, C. tetani, B. perussis,* Hepatitis B virus, Poliovirus	Toxoid, subunit	[317]
Diphtheria, tetanus, pertussis (acellular), hepatitis B, poliovirus (inactivated) and Hib	NA[f]	*C. diphtheria, C. tetani, B. pertussis,* Poliovirus, Hepatitis B virus, Hib	Toxoid, subunit	[237]
Diphtheria, tetanus, pertussis (acellular), poliovirus (inactivated) and Hib	Pentacel	*C. diphtheriae, C. tetani, B. pertussis,* Poliovirus, Hib	Toxoid, inactivated, killed, conjugated	[319]
Diptheria, tetanus, pertussis (acellular) and poliovirus (inactivated)	Kinrix, Quadracel	*C. diphtheriae, C. tetani, B. pertussis,* Poliovirus	Toxoid, subunit	[238, 318]
Diphtheria, tetanus, pertussis (whole cell), hepatitis B and Hib	NA[g]	*C. diphtheriae, C. tetani, B. pertussis,* Hepatitis B virus, Hib	Toxoid, inactivated, subunit	[239–247]
Diphtheria, tetanus, pertussis (whole cell) and hepatitis B	NA[h]	*C. diphteriae, C. tetani, B. perussis,* Hepatitis B virus	Toxoid, inactivated, subunit	[248]

(continued)

Table 4.5 (continued)

Vaccine	US trade name(s)	Infectious agent(s) covered	Vaccine type	Resources
Diphtheria, tetanus, pertussis (whole cell) and Hib	NA[i]	*C. diphtheriae, C. tetani, B. pertussis,* Hib	Toxoid, inactivated, subunit	[249, 250]
Enterotoxigenic *Escherichia coli* (ETEC), Cholera	NA[j]	ETEC, *V. cholerae*	Inactivated, subunit	[349]
Hib	ActHIB, HIBERIX, Pedvax HIB[k]	Hib	Subunit	[81–83, 251, 252]
Hepatitis A	HAVRIX, VAQTA	Hepatitis A virus	Killed	[104, 105]
Hepatitis A and Hepatitis B	Twinrix	Hepatitis A virus, Hepatitis B virus	Killed, subunit	[110]
Hepatitis B	ENGERIX-B, RECOMBIVAX HB[l]	Hepatitis B virus	Subunit	[1, 73, 253–258]
Hepatitis E	NA[m]	Hepatitis E virus	Subunit	[259]
HPV Quadrivalent	Gardasil	HPV types 6, 11, 16, and 18	Subunit	[321]
HPV 9-Valent	Gardasil 9	HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58	Subunit	[162]
Influenza, seasonal, quadrivalent	FLUARIX QUADRIVALENT, FLUCELVAX QUADRIVALENT, FluLaval Quadrivalent, Fluzone high-dose, Fluzone Quadrivalent, Fluzone Quadrivalent Intradermal	Seasonal influenza types A and B	Subunit	[322–324, 326, 327, 329]
Influenza, seasonal, trivalent	AFLURIA, FLUAD, FLUBLOK, FLUVIRIN Fluzone, Fluzone high-dose[n]	Seasonal influenza types A and B	Subunit	[320, 325, 328, 330–333]
Japanese encephalitis	IXIARO, JE-VAX[o]	Japanese encephalitis virus	Killed or live	[260–262, 334, 335]
Measles	NA[p]	Measles virus	Live	[263–265]
Measles and rubella	NA[q]	Measles virus and rubella virus	Live	[266]

Measles, mumps and rubella	MMR-II[r]	Measles virus, mumps virus, rubella virus	Live	[59, 267, 268, 336]
Measles, mumps, rubella and varicella	ProQuad	Measles virus, mumps virus, rubella virus, varicella virus	Live	[269]
Meningococcal group A	NA[s]	*N. meningitidis* group A	Subunit	[270, 271]
Meningococcal group B	Trumenba; BEXSERO	*N. meningitidis* group B	Subunit	[149, 150]
Meningococcal groups A and C	NA[t]	*N. meningitidis* groups A and C	Inactivated	[272, 273]
Meningococcal groups A, C, Y, W-135	Menactra, MENVEO, Menomune	*N. meningitidis* groups A, C, Y, W-135	Subunit	[141, 274, 350]
Pneumococcal	Prevnar	*S. pneumoniae* serotypes 4, 6B, 9 V, 14, 18C, 19F, 23F	Subunit	[351]
Pneumococcal	NA[u]	*Streptococcus pneumoniae* serotypes 1, 4, 5, 6B, 7F, 9 V, 14, 18C, 19F, 23F	Subunit	[275]
Pneumococcal	Prevnar-13	*S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9 V, 14, 18C, 19A, 19F, 23F	Subunit	[276]
Pneumococcal	Pneumovax23	*S.pneumoniae serotypes* 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F	Killed	[337]
Poliovirus, inactivated	IPOL[v]	Poliovirus	Killed	[277–281]
Poliovirus, bivalent types 1 and 3, oral	NA[w]	Poliovirus	Live	[282–286]
Poliovirus, monovalent type 1, oral	NA[x]	Poliovirus	Live	[338–340]
Poliovirus, monovalent type 2, oral	NA[y]	Poliovirus	Live	[288, 289]
Poliovirus, monovalent type 3, oral	NA[z]	Poliovirus	Live	[287]

(continued)

Table 4.5 (continued)

Vaccine	US trade name(s)	Infectious agent(s) covered	Vaccine type	Resources
Poliovirus, trivalent, oral	NA[aa]	Poliovirus	Live	[290–293, 341]
Rabies	RabAvert, Imovax Rabies[ab]	Rabies virus	Killed	[294–298]
Rotavirus	ROTARIX, RotaTeq	Rotavirus	Live	[299, 300]
Rubella	NA[ac]	Rubella virus	Live	[301]
Small pox	ACAM2000	Small pox virus	Live	[302]
Tetanus and diphtheria	DECAVAC, TENIVAC, Tetanus and Diphtheria Toxoids, Absorbed[ad]	*C. diphtheriae, C. tetani*	Toxoid	[18, 231, 232, 342, 343]
Tetanus, diphtheria and pertussis (acellular)	Adacel, BOOSTRIX	*C. diphtheriae, C. tetani, B. pertussis*	Toxoid, subunit	[16, 17]
Tetanus	NA[ae]	*C. tetani*	Toxoid	[303–308]
Tick-borne encephalitis	NA[af]	TBE virus	Killed	[309, 344, 345]
Typhoid	Typhim Vi, Vivotif	*S. typhi*	Inactivated or live	[310, 311]
Varicella (chicken pox)	VARIVAX	VZV	Live	[91]
Yellow fever	YF-VAX[ag]	Yellow fever virus	Live	[312–316]
Zoster	ZOSTAVAX	VZV	Live	[172]

[a]BCG freeze-dried glutamate vaccine; BCG vaccine; BCG vaccine (freeze dried) – intradermal; BCG vaccine SSI
[b]Euvichol; Shanchol
[c]Dengvaxia (CYD-TDV)
[d]Adsorbed DT vaccine; Diftet; diphtheria and tetanus vaccine adsorbed, pediatric; DT VAX
[e]Diphtheria-tetanus-pertussis vaccine adsorbed; DTP vaccine
[f]Hexaxim
[g]Diphtheria, tetanus, pertussis, hepatitis B, and Haemophilus influenzae type b conjugate vaccine; diphtheria, tetanus, pertussis, hepatitis B, and Haemophilus influenzae type b conjugate vaccine adsorbed; Euforvac-Hib injection; Eupenta; Easyfive-TT; Pentabio; Quinvaxem; Shan-5; Tritanrix HB + Hib
[h]Diphtheria, tetanus, pertussis, and hepatitis B vaccine adsorbed; DTP-Hep B 5; DTP-Hep B 10
[i]Diphtheria, tetanus, pertussis, and Haemophilus influenzae type b conjugate vaccine; TETRAct-HIB

[j]Dukoral
[k]Haemophilus influenzae type b vaccine; Vaxem HIB
[l]Euvax B; Heberbiovac HB; hepatitis B vaccine recombinant; hepatitis B vaccine (rDNA) (adult); hepatitis B vaccine (rDNA) (Ped); Hepavax; Hepavax-Gene TF; Shanvac-B
[m]Hecolin
[n]GC FLU; influenza vaccine (split virion, inactivated); Nasovac-S; Vaxigrip
[o]JEEV; IMOJEV MD; Japanese encephalitis vaccine live (SA14–14-2)
[p]Measles vaccine; measles vaccine, live, attenuated; ROUVAX
[q]Measles and rubella virus vaccine live
[r]PRIORIX; TRIMOVAX MÉRIEUX
[s]MenAfriVac; MenAfriVac 5 µg
[t]Polysaccharide meningococcal A + C; polysaccharide meningococcal A + C
[u]Synflorix
[v]IMOVAX POLIO; IPV vaccine SSI; poliomyelitis vaccine; Poliorix
[w]BIOPOLIO B1/3; bivalent oral poliomyelitis vaccine type 1 and 3; bivalent type 1 and 3 oral poliomyelitis vaccine, IP; Polio Sabin One and Three; bivalent types 1 and 3 oral polio vaccine for children
[x]Monovalent type 1 oral poliomyeltis vaccine, IP; oral monovalent type 1 poliomyelitis vaccine; Polio Sabin Mono T1
[y]Oral monovalent type 2 poliomyelitis vaccine (nOPV2); Polio Sabin Mono Two (oral)
[z]Oral monovalent type 3 poliomyelitis vaccine; Polio Sabin Mono T3
[aa]BIOPOLIO; OPVERO; oral polio; poliomyelitis vaccine (oral) trivalent types 1, 2 and 3; polioviral vaccine
[ab]Rabies vaccine; Rabipur; VERORAB
[ac]Rubella vaccine, live, attenuated
[ad]IMOVAX dT
[ae]ShanTT; tetanus adsorbed vaccine BP; tetanus toxoid; Tetatox; TETAVAX; TT vaccine
[af]FSME-IMMUN; FSME-IMMUN (Junior); Encepur; Encepur-K; TBE-Moscow; EnceVir
[ag]Stabilized yellow fever vaccine; STAMARIL; yellow fever; yellow fever vaccine, live

booster dose; however, a small study demonstrated a strong antibody response, higher than seen with primary vaccination [146, 147].

In response to college outbreaks of serogroup B meningococcal disease, the Food and Drug Administration (FDA) fast tracked approval of two serogroup B meningococcal vaccines [148]. Trumenba® is a two- or three-dose series and was the first serogroup B meningococcal vaccine licensed in 2014 [149]. One year later, Bexsero® was licensed as a two-dose series against serogroup B vaccine [150]. As with the conjugate meningococcal processors, the serogroup B vaccine efficacy was based on immune response [148]. Trumenba® immunogenicity response was evaluated when given concomitantly with a HPV vaccine versus with placebo. Protective antibody levels following one month after three doses of Trumenba® ranged from 88.5% to 99.4%, depending on heterologous variant of serogroup B strain; the immune response was more robust after three doses compared to two doses [151]. Antibody titers rapidly declined after the three-dose series, but stabilized after 6 months, and antibody titer protection was demonstrated in more than 50% of subjects four years after vaccine series [152]. Following one dose of Bexsero®, protective antibody levels were evident in 92–97% of adolescents, increasing to almost 100% after two doses, and minimal difference was seen when three doses were given [153]. Protective immunogenicity of Bexsero® against three serogroup B strains 18–24 months after a single dose decreased to 62–73%, after two doses to 77–94%, and after three doses to 86–97% [154]. The sustained impact of these fast-tracked vaccines against serogroup B meningococcal disease remains to be seen.

Human Papillomavirus

Human papillomavirus (HPV) is a sexually transmitted small DNA virus with over 100 distinct types, 35–40 of which are known to infect the skin and mucous membranes of the anogenital region. CDC estimates that HPV accounts for the majority of newly acquired sexually transmitted infections in the USA with recent data indicating nearly 80 million new and existing HPV infections. HPV is the most common sexually transmitted infection in the USA [155].

Most HPV infections are asymptomatic and do not progress to disease, as the body's immune system clears approximately 90% of infections within 2 years. Low-risk HPV genotypes can lead to genital warts, whereas persistence of high-risk types can lead to many types of cancer including cervical cancer, other anogenital cancers, and cancers of the head and neck [156].

Based on CDC data from 2008 to 2012, approximately 38,793 HPV-associated cancers occur in the USA annually; 23,000 among women and 15,793 among men. HPV is thought to be responsible for more than 90% of anal and cervical cancers, about 70% of vaginal and vulvar cancers, and more than 60% of penile cancers. Approximately 70% of head and neck cancers may be linked to HPV and may be associated with a combination of tobacco, alcohol, and HPV. In 2015, the prevalence

of genital warts reported in patients who presented to sexually transmitted disease (STD) clinics (as reported by the STD Surveillance Network) shows the highest rates of genital warts in men who have sex with women (MSW) 4.3% (range 1.7–8.1), followed by men who have sex with men (MSM) 3.3% (range 1.9–4.6) and women 0.9% (range 0.7–2.2). HPV types 16 and 18 are known to cause the vast majority of disease and have been implicated in approximately 70% of cases of cervical carcinoma. Clearance rates in women in the USA have been cited as high as 70–100% at 2–5 years and are highest in young women and in those with non-oncogenic genotypes. Women of low socioeconomic status and in developing countries are disproportionately affected, likely due to lower screening rates and availability of HPV vaccines. In 2012, over 200,000 women worldwide died of cervical cancer, 85% of them in developing countries. HPV has been detected in 99.7% of cases of cervical carcinoma, approximately 90% of anal cancers, 40% of vulvar and vaginal cancers, 40% of penile cancers, and 25% of cancers of the head and neck [157].

Human Papillomavirus Vaccine and Vaccine Efficacy

HPV vaccine is recommended for preteen boys and girls at age 11 or 12 so they are protected before exposure to the virus. A more robust immune response is seen in younger preteen patients than in older teens and young adults. The HPV vaccine is given in a two- or three-dose series depending on the patients' age. For patients under 15 years of age, the recommendation is for two doses, 6–12 months apart. For patients ≥15 years of age, the recommendation is for three doses at 0, 1–2, and 6 months of age [158].

Gardasil® was licensed in 2006 as a quadrivalent vaccine against HPV types 6, 11, 16, and 18 [13]. The Females United to Unilaterally Reduce Endo/Ectocervical Disease (FUTURE) II trials demonstrated 100% efficacy against anogenital warts and vulvar or vaginal intraepithelial neoplasia or cancer related to HPV types 6, 11, 16, and 18. The FUTURE II trial also demonstrated 98% prevention of cervical intraepithelial neoplasia grade 2 or 3 or cervical adenocarcinoma in situ related to HPV types 16 and 18 related in HPV-naïve females aged 15–26 years after three doses of quadrivalent vaccine with Gardasil® in greater than 95% of subjects [159, 160]. Gardasil® was approved for use in males in 1999. The prevention of external genital warts; penile, perianal, or perineal intraepithelial neoplasia; or penile, perianal cancer related to the four types contained in the vaccine of the per-protocol population was 90.4% for males ages 16–26 [161].

In 2014, a 9-valent HPV vaccine, Gardasil®9, was licensed to protect against the same diseases and precancerous or dysplastic lesions as Gardasil®, with expanded coverage of five additional HPV virus types [31, 33, 45, 52, 58, 162]. The addition of these five types could lead to an additional 14.7% protection from invasive cervical cancer [163]. The Broad Spectrum HPV Vaccine Study demonstrated 96.7% risk reduction of high-grade cervical, vulvar, and vaginal disease, caused by HPV types

31, 33, 45, 52, and 58 in HPV-uninfected females aged 16–26 years after three doses of Gardasil®9 within one year of enrollment [164]. Immunobridging studies were utilized to establish Gardasil®9 efficacy via noninferiority in the following groups: adolescent females aged 9–15 years and males aged 16–26 years. Notably, male and female adolescents (aged 9–15 years) had significantly higher antibody titers to Gardasil®9 compared to females aged 16–26 years receiving the 9-valent HPV [165]. Post clinical trial efficacy data is gradually being published. A 6.1% decrease in prevalence of HPV types 6, 11, 16, and 18 in females aged 14–19 years was demonstrated in those having received three doses (62.5%) of Gardasil® [166]. The impact of HPV vaccination on the incidence and mortality rate of cervical cancer has yet to be determined [167].

Varicella Zoster Virus: Shingles

Varicella zoster virus (VZV) not only causes varicella, but also causes herpes zoster (HZ), or shingles. Shingles occurs following reactivation of latent VZV of cranial nerves or dorsal root ganglia. Approximately 1 million cases of HZ occur annually in the USA, and incidence increases with age; 68% of HZ cases occur in persons over age 50. Almost one out of every three people in the USA will develop shingles in their lifetime [168]. Both natural VZV infection and vaccination against VZV with live, attenuated virus result in latent virus acquisition. Those who are immunized against varicella show decreased shingles incidence than those who acquired the disease naturally [169].

Shingles is characterized by a painful maculopapular or vesicular rash, usually unilateral and following one or two adjacent dermatomes. Less commonly the rash can be more widespread and affect three or more dermatomes; this condition is known as disseminated zoster [170]. The most commonly involved dermatomes include V1 of the trigeminal nerve and the thoracic nerves T1–L2. Approximately 1–4% of people who get shingles are hospitalized for complications, and each year there are approximately 96 shingles-related deaths in the USA [171].

Other complications of shingles include secondary bacterial infections, herpes zoster ophthalmicus, a complication that can lead to blindness without appropriate treatment, aseptic meningitis, transverse myelitis, stroke symptoms, and postherpetic neuralgia (PHN). Prevalence of PHN in the USA is estimated at greater than 500,000.

PHN, with pain persisting over the area of the shingles rash for more than 30 days, is one of the most devastating and common sequelae of shingles infection. PHN can significantly affect quality of life and ability to perform activities of daily living. Its incidence increases with age. Approximately 13% of people 60 years of age and older with zoster will get PHN [170].

Varicella Zoster Virus: Shingles Vaccine Efficacy

Zostavax®, the zoster live attenuated virus vaccine licensed in 2006, is indicated for prevention of herpes zoster [172]. It is approved by FDA for people 50 years of age and older but recommended by ACIP for people 60 years of age and older whether or not they report a prior episode of shingles or prior history of chicken pox.

In the Shingles Prevention Study, overall zoster vaccine efficacy of 51.3% was demonstrated against HZ in patients over 60, with the greatest efficacy occurring in patients 60–69 years old (63.9%), declining by roughly 20% each decade thereafter. Vaccine efficacy to reduce the incidence of PHN varied among age groups, with the highest efficacy (55%) in subjects aged 70–79, followed by those greater than 80 years old (26%). The lowest efficacy of PHN was observed in subjects aged 60–69 at 5% [172, 173]. The Zostavax® Efficacy and Safety Trial found subjects aged 50–59 had a vaccine efficacy between 69.8% and 72.4% [174]. Studies assessing the duration of efficacy suggest a decline in protection after 8 years to 21.1% or less [175]. The ACIP recommendation for zoster vaccination 10 years after current FDA-licensed approval age is due to these studies showing waning protection [176]. Despite the herpes zoster vaccine reduction of 50–60% disease incidence and sequelae, further innovation for a more effective herpes zoster vaccine remains to be seen, especially with the expected increase in the geriatric population [177].

Overview of Vaccine Types

The characteristics of the pathogen targeted by a vaccine determine the type of vaccine that can be produced to protect humans from acquiring the targeted disease or illness. There are currently four major types of vaccines: live attenuated, inactivated, toxoid, and subunit vaccines.

Live Attenuated

A live, attenuated vaccine contains a non-virulent, living version of the pathogen against which it protects. These weakened, or attenuated, pathogens have lost the ability to infect or replicate in a human host, but still elicit an immune response. Methods for attenuating pathogens vary, but involve selectively culturing generations of the pathogen with progressively limited ability to replicate in a human host. This is most readily achieved in viruses, with their rapid replication and mutation rates [178–180].

Live, attenuated vaccines elicit a strong immunological response, with typically long-lived protection. However, there are risks to the use of live vaccines. An immunologically incompetent host may have an insufficient immune response to the vaccine

to prevent subsequent illness from the attenuated pathogen. Alternatively, as the live pathogens retain the ability to mutate, they may regain their virulence in humans. Additionally, live, attenuated vaccines are the least stable vaccine type, often requiring refrigeration [178–180].

Inactivated

Killed or inactivated vaccines are an alternative to live, attenuated vaccines. (The word *killed* is usually used to refer to bacterial pathogens, while *inactivated* is used to refer to viruses.) Like attenuated vaccines, inactivated vaccines contain the whole disease-causing pathogen or microbe. Killing, or inactivation, is a result of exposure to heat, radiation, or chemicals such as formaldehyde and formalin. The pathogen that remains following inactivation allows for an immunologic response to a wide array of surface antigens [178]. The killed pathogen cannot revert or mutate to a more virulent form and cause illness or disease. However, the immunologic response to killed or inactivated vaccines is less robust and provides a shorter length of duration of protection than the response to live, attenuated vaccines and typically requires multiple doses, boosters, and/or adjuvants to promote a good immunologic response and maintain protection.

Toxoid

A toxoid is a bacterial toxin, usually an exotoxin, whose toxicity has been inactivated or suppressed either by heat or chemicals that can still produce an immunologic response. Toxoid vaccines carry no risk of infection; however, they generally produce a weak immune response, and therefore multiple doses, boosters, and/or adjuvants are typically required to induce immunity [178]. Tetanus and diphtheria vaccines are examples of toxoid vaccines.

Subunit

Subunit vaccines use specific antigens, or epitopes of antigens, of the targeted pathogen to invoke an immune response. Subunit vaccines can be further subdivided into conjugate, recombinant, and viruslike particle vaccines. In conjugate vaccines, a polysaccharide antigen, which typically elicits a weak immune response, is covalently bound to a strongly immunogenic carrier protein. The carrier protein allows for a more efficient immune response to the polysaccharide antigen, conferring immunity to the targeted pathogen [178, 179].

Recombinant vaccines are produced through recombinant DNA technology. They may be classified as either DNA vaccines or recombinant (protein subunit) vaccines. These types of vaccines use genetic material coding protein antigens from a targeted pathogen that stimulates the immune response that are then inserted into microbial DNA cells of the body. As the host cell reproduces, the protein antigen of the pathogen is expressed and can be used to induce an immunologic response to the targeted pathogen. An example of a recombinant protein vaccine is the HepB vaccine.

Viruslike particle vaccines are similarly created with recombinant DNA technology. The selected viral protein antigens of these vaccines mimic the organization and conformation of authentic native viruses, but without the native viral genome, thus prompting an immune response to the expressed protein in a potentially safer and cheaper manner than other subunit vaccines [179–181]. While there is no risk of virulence or illness with subunit vaccines, there are disadvantages to their use. Often subunit vaccines require multiple doses, boosters, and/or adjuvants to produce sufficient immunity. Additionally, local reactions at the site of vaccination are common [178].

Indications for Routine Vaccine Recommendations

CDC has established routine vaccination recommendations for children and adults and recommendations for people with special conditions, for travelers, for those with certain occupations and exposures and during outbreaks.

Pediatric Vaccine Schedule

Presently, vaccines are recommended by ACIP against 13 diseases for all children and adolescents aged 0 through 18 years, in addition to an annual influenza vaccine recommendation. The first dose in the series of the HepB vaccine is the only vaccine given immediately postpartum, before hospital discharge. This early administration ensures that newborns born to mothers unaware they are infected with HBV will be spared severe illness and possible death if the virus is transmitted during delivery [182]. Two additional doses of HepB are recommended to confer full immunity, the second at 1–2 months of age and the third at 6–18 months of age.

Six vaccines are recommended for children at 2 months of age: HepB, rotavirus, DTaP, Hib, pneumococcal conjugate, and inactivated poliovirus. At 4 months of age, second doses of all of the vaccines given at 2 months of age (except for HepB) are recommended [183].

The type of vaccine administered guides the number of doses required. There are two rotavirus vaccines: the RV1 is a two-dose series while the RV5 has an additional third dose that should be given at 6 months of age. Depending upon the brand of Hib vaccine administered, three doses are sufficient at 2, 4, and 6 months, and a forth dose may be needed at 12–18 months of age. There are currently six Hib vaccines

approved for use, three of them are combined with vaccines for other diseases and three of them solely confer vaccination against Hib. Each brand of the Hib vaccine needs to be assessed for the number of doses required [183].

Three additional vaccines recommended to be completed by 6 years of age include DTaP, the pneumococcal conjugate, and inactivated poliovirus vaccines. The DTaP vaccine has a recommended total of five doses through age 6. Three doses at 2, 4, and 6 months of age, one dose at 15–18 months of age, and one dose at 4–6 years of age are recommended. Four doses of the pneumococcal conjugate at 2, 4, 6, and 12–18 months are recommended, and inactivated poliovirus vaccine is recommended at 2, 4, and 6–19 months and 4–6 years of age [183].

MMR, VZV, and HepA vaccines are not recommended until after 1 year of age. The first dose of each of these vaccines should be administered at 12–18 months of age. The second doses of MMR and varicella vaccines should be administered at 4–6 years of age. HepA vaccine has a more specific instruction as to when its second dose should be administered; it needs to be 6–18 months after the initial dose [183].

Immunizations for those over age 6 include TdaP, meningococcal, and HPV vaccines.

Tdap is recommended for children aged 7 through 18 years who are not fully vaccinated, preferentially at 11–12 years of age along with meningococcal and HPV vaccines. A booster dose of meningococcal vaccine should be administered at 16 years of age. The meningococcal B vaccine is not routinely recommended, but it is available as a permissive recommendation and can be administered at a clinician's discretion. A two- to three-dose series of HPV vaccine are recommended on a schedule of 0 and 6–12 months to be completed by 13 years of age (up to age 15) and on a schedule of 0, 1–2, and 6 months if the series is started after age 15 [183].

The influenza vaccine is the only vaccine recommended to be given annually to all individuals 6 months of age and older. For each influenza season, there are usually several vaccine types available. Young children under 8 years of age require two doses of the influenza vaccine administered at least 4 weeks apart the first time they are vaccinated against influenza. Note: influenza recommendations are unique to each influenza season, and the annual recommendation should be referenced each year [184].

Adult Vaccine Schedule

The routine adult vaccine schedule includes vaccines against tetanus, diphtheria, pertussis, varicella, zoster, and pneumococcal diseases. Tdap is given once after 19 years of age, and then a Td booster is recommended once every 10 years thereafter. Adults without evidence of immunity to varicella should receive two doses of varicella vaccine. Evidence of immunity includes documentation of two doses of varicella vaccine at least 4 weeks apart, USA born before 1980 (excluding healthcare personnel and pregnant women), history of varicella disease, history of herpes zoster, laboratory evidence of immunity, or laboratory confirmation of disease. The human papillomavirus vaccine is only recommended in adulthood through 26 years of age, if the vaccine series was not completed during adolescence.

In addition to an annual influenza vaccine, adults over the age of 60 years are recommended to receive a single dose of zoster vaccine regardless of whether they have had chicken pox or a prior episode of herpes zoster. All adults over the age of 65 should receive the PCV13 vaccine and at least 1 year later PPSV23 vaccine.

Vaccine Recommendations for Special Populations

Pregnant Women

Pregnant women should receive a Tdap vaccine with each pregnancy during their third trimester. It is also important to vaccinate pregnant women anytime during pregnancy with influenza vaccination [185, 186]. Rubella and varicella immunity should be assessed. Pregnant women without immunity are to be administered needed MMR and varicella vaccines postpartum before discharge from hospital. Second doses of each vaccine are to be given 4 weeks later. The following live vaccines are contraindicated for pregnant women, varicella, zoster, and MMR, because a risk to the fetus cannot be excluded. HPV vaccine is not recommended during pregnancy.

Immunocompromised Patients

Individuals who have HIV infection should receive vaccine recommendations based upon their CD4+ count. Those with a CD4+ count greater than or equal to 200 (cells/microliter) are no longer contraindicated to receiving live vaccines. All immunocompromised patients are recommended to receive the pneumococcal PCV13 and PPV23 vaccines. Individuals who have received a hematopoietic stem cell transplant (HSCT) should receive a three-dose regimen of the Hib vaccine starting at 6–12 months after a successful transplant. The doses should be separated by at least 4 weeks and given regardless of the patient's vaccination history. Of immunocompromised individuals, only HIV-infected individuals are recommended to receive the hepatitis B vaccine (regardless of CD4+ count). It is important to reference CDC recommendations for the most up-to-date and specific information for immunocompromised patients. Immunocompromised individuals should not receive the three live vaccines: varicella, zoster, and MMR [186].

Men Who Have Sex with Men (MSM)

The hepatitis A and B vaccines are recommended for men who have sex with men. Two doses of HepA vaccine should be given 6 months apart, and three doses of HepB or a combination HepA/HepB given at 0, 2, and 6 months are recommended. For MSM younger than 26 years, three doses of HPV vaccine are recommended at 0, 1–2, and 6 months.

Healthcare Personnel

In addition to the normally recommended vaccine schedule, healthcare workers should receive the HBV series as they could potentially be exposed to infectious blood or body fluids. Additional vaccines may be recommended depending upon what type of healthcare work is performed. Measles, mumps, rubella, and varicella immunity should be assessed, and if not present, appropriate immunizations should be given.

Other Medical Conditions/Indications

For persons with unique medical conditions, specific vaccines may be recommended. These conditions include chronic diseases such as diabetes, heart disease, chronic lung disease (including asthma), kidney disease, liver disease, and alcoholism. All persons with the afore-listed conditions and diseases are recommended to receive one PPSV23 vaccine prior to age 65. In addition, diabetics and those with chronic liver or kidney disease are additionally recommended to complete the HBV vaccination series; those with liver disease are recommended to receive the HAV series as well. For those with chronic kidney disease, one dose of PCV13 before age 65 is also indicated. Full recommendations from CDC may be found at: https://www.cdc.gov/vaccines/schedules/hcp/imz/adult-conditions.html.

Contraindications to Vaccines

In addition to the contraindications for specific populations highlighted above, severe allergic reaction (e.g., anaphylaxis) experienced after receiving a vaccine dose or a known anaphylactic allergy to a vaccine component of any vaccine is a contraindication to receiving doses of that vaccine. Based on 2016 CDC recommendations, people with egg allergies no longer need to be observed for an allergic reaction for 30 min after receiving a flu vaccine. There is a common misconception that people with mild to moderate egg allergies should not receive influenza vaccines. Persons with a history of egg allergy who have experienced only hives after exposure to egg should receive flu vaccine: any licensed and recommended flu vaccine (i.e., any form of IIV or RIV) 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 flu vaccine (i.e., any form of IIV or RIV) that is otherwise appropriate for the recipient's age and health status. For those with severe egg allergies, the influenza 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 healthcare provider who is able to recognize and manage severe allergic conditions [187].

Postexposure Prophylaxis

Postexposure prophylaxis (PEP) is defined as "a preventive measure taken to protect a person or community from harm after contact with disease-causing chemicals, germs, or physical agents." [188] PEP in the form of vaccines or immunoglobulin (IG) is routinely recommended following exposure to many viral and bacterial diseases.

Viral Hepatitides

Hepatitis A

Hepatitis A is spread to others via close personal contact (household and sex contacts), illicit drugs, and food preparation. Recently exposed people who have not been vaccinated previously should be given the HepA vaccine or IG within 2 weeks after exposure. IG is the recommended treatment for people at increased risk of severe HepA infection, such as the elderly and those who are immunocompromised [189].

After exposure to HAV:

- Healthy persons aged 12 months to 40 years should receive the HepA vaccine (preferred) or immunoglobulin (IG) to be administered within 2 weeks of exposure.
- For those over 40 years old, give IG.
- Give IG for children less than 12 months, immunocompromised persons, or those with chronic liver disease [190].

Hepatitis B

Hepatitis B is spread via exposure to blood or body fluids. After exposure to HBV, timely prophylaxis can prevent HPV infection. The mainstay of PEP is HepB vaccine, but in certain circumstances, HepB IG is recommended in addition to vaccination [191].

For an exposure to a known hepatitis B surface antigen (HBsAg)-positive source:

- Persons who have completed the HepB vaccine series but did not receive post-vaccination testing should receive a single vaccine booster dose.

- Persons in the process of being vaccinated but have not completed the series should receive the appropriate dose of HepB IG (HBIG) and complete the vaccine series.
- Unvaccinated persons should receive both HBIG and HepB vaccine as soon as possible after exposure (preferably within 24 h). The vaccine may be administered simultaneously with HBIG in a separate injection site.

For an exposure to a source with unknown HBsAg status:

- Persons with written documentation of a complete HepB vaccine series require no further treatment.
- Persons who are not fully vaccinated should complete the vaccine series.
- Unvaccinated persons should receive the HepB vaccine series with the first dose administered as soon as possible after exposure, preferably within 24 h [192].

Note:

- For one previously vaccinated with adequate response, no PEP is indicated.
- For a person who is vaccinated with the HepB series once, but a non-responder, a single dose of HBIG is recommended within hours of exposure, followed by the vaccine series.
- For one who is vaccinated and a non-responder after two vaccination series, give HBIG twice within 24 h of exposure [193].

Hepatitis C

Hepatitis C is spread via large or repeated percutaneous exposures to infectious blood. This may occur though injection drug use (the most common means of transmission in the USA currently), receipt of donated blood or organ (now rare in the USA since blood screening began in 1992), through needlestick injuries in the healthcare settings, and during childbirth in a hepatitis C-infected mother. Unfortunately, there is no PEP that has been proven useful after a hepatitis C exposure [194, 195]. An experiment with chimpanzees given IG prior to a needlestick with hepatitis C-positive blood did not prevent the transmission of infection. Additional research has similarly shown that no protective antibody response has been induced to prevent infection.

HIV

After exposure to HIV, short-term antiretroviral therapy is indicated. No vaccine is available.

Note: There exists preexposure prophylaxis, or PrEP, to prevent HIV infections for those that are at substantial risk of getting HIV. A daily pill (taken consistently) containing two medications, tenofovir and emtricitabine, has been shown to reduce the risk of HIB infection in people who are at high risk by up to 92% [196, 197].

Influenza

PEP is recommended for people that have a high risk of complications from an influenza infection who have had contact with an ill individual from 1 day prior to influenza symptoms onset until 1 day after defervescence [195]. Those at a high risk might include those unable to receive the vaccine, exposure during the 2 weeks after influenza immunization, and family members or healthcare providers who are unimmunized and likely to have close exposure to unimmunized infants and toddlers. Chemoprophylaxis can be used in addition to immunization in children who may not respond well to the vaccine or in instances when the circulating strains of influenza virus in the community are not well matched with the seasonal influenza vaccine strains [198]. Widespread or routine use of antiviral medications chemoprophylaxis is not recommended as it could encourage the emergence of antiviral resistant viruses. Oseltamivir and zanamivir are the two antiviral medications used for PEP. Oseltamivir is approved for use in children older than 3 months of age, and zanamivir is approved for use in children 5 years of age or older. It is recommended that chemoprophylaxis be given for 7 days after the last known exposure. However, if more than 48 h have elapsed since the initial exposure to the infectious person, antiviral chemoprophylaxis is not generally recommended [199].

Measles

The most vulnerable to a measles exposure include those unvaccinated or under vaccinated, infants under 12 months of age who would have not yet received the vaccine, pregnant women without evidence of immunity, and immunocompromised people.

- If exposed to measles, the MMR vaccine must be administered within 72 h of the exposure to be effective.
- If the timeframe is missed or if a person is unable to receive the vaccine, IG can be given intramuscular (IM) or intravenous (IV) within 6 days of exposure to help prevent or limit measles infection.
- IG IM is the recommended prophylaxis treatment for children under 12 months of age since they cannot receive the MMR vaccine.
- Pregnant women and severely immunocompromised people should receive IG IV since they cannot receive the MMR vaccine [198].

Meningococcal Disease

Whether vaccinated with meningococcal vaccines or not, anyone who has had close contact with an infected individual with meningococcal disease within the 7 days prior to onset of illness should be treated [200]. Antibiotic prophylaxis should be

initiated within 24 h after the infectious patient has been identified [201]. Effective antibiotic regimens may include ceftriaxone, rifampin, or ciprofloxacin. Ceftriaxone is the regimen of choice for pregnant women. Azithromycin is not routinely recommended as a treatment choice, but could be used if needed [198].

Pertussis

The CDC recommends targeting postexposure antibiotics against pertussis to high-risk individuals and people who have close contact with high-risk individuals. PEP can be administered to contacts within 21 days of exposure to onset of cough in the index case. People who are at high risk include all household contacts, infants, women in the third trimester of pregnancy, and persons with preexisting health conditions. Asthma or immunocompromised conditions such as moderate-to-severe asthma may be exacerbated by a pertussis infection [198, 202]. Household contacts (including immunized contacts) should be treated because secondary attack rates are high. Extensive contact tracing and broadscale use of postexposure antibiotics are not effective uses of public health resources, and there is no data to indicate that widespread use of PEP among contacts will effectively control or limit the scope of a pertussis outbreak. All unimmunized or under-immunized contacts should be vaccinated [202].

The preferred antibiotic treatment for PEP in persons older than 1 month includes erythromycin, clarithromycin, and azithromycin. For those younger than 1 month, only azithromycin is recommended. An alternative that is available for patients 2 months and older is trimethoprim/sulfamethoxazole [203].

Rabies

Each year approximately 16,000–39,000 people receive rabies PEP after coming into contact with a potentially rabid animal [204]. Indications for rabies PEP include being bitten or scratched by a suspected rabid animal or when a reliable history of exposure cannot be obtained. For example, if a person awakens in a room to find a bat in the room, PEP may be considered, as contact between the bat through the person's mucous membrane (lips) and the bat cannot be excluded. Treatment can be discontinued if a suspected rabid animal is quarantined and remains healthy for 10 days or if the animal is humanely killed and tests negative for rabies [205]. It is important to treat patients exposed to rabies with PEP because treatment of clinical rabies is an extreme challenge and only one person has recovered from rabies without receiving PEP [204].

Wound cleansing is the first step of PEP. It is especially important because wound cleansing alone without any further PEP has shown a marked reduction in the likelihood of rabies. The recommendations for rabies PEP are the following:

- Those who have not previously received the rabies vaccine should be given both passive antibody and vaccine. Unvaccinated individuals should receive rabies vaccine on days 0, 3, 7, and 14 (a fifth dose on day 28 if immunocompromised). Human rabies IG should be administered around the wound if anatomically feasible, with the rest into the gluteal region.
- Those previously vaccinated with rabies vaccine series should only be readministered the vaccine: only two doses of vaccine (days 0 and 3) are necessary if there is evidence of protective neutralizing antibodies [206].

Tetanus

Puncture wounds, compound fractures, burns, unsterile injections, and crush injuries or wounds with potential contamination with dirt or rust are possible indications for tetanus PEP. If a person is uncertain of their vaccination history or did not complete a three-dose primary series of tetanus-containing vaccine, they should receive a tetanus vaccine and a single dose of tetanus IG.

- For minor and clean wounds, a person should receive a tetanus vaccine if their most recent dose was given more than 10 years ago.
- For puncture wounds or wounds contaminated with dirt, a tetanus vaccine is indicated if their most recent dose was more than 5 years ago [195].

Tuberculosis

Tuberculosis (TB) bacteria are put into the air when a person with TB disease of the lungs or throat coughs, speaks, or sings [207]. Anyone nearby could breathe in these bacteria and therefore should receive PEP. Even if a person previously received bacilli Calmette-Guérin (BCG) immunization or has their own tuberculosis history, they should still receive PEP. A tuberculin skin test or interferon gamma release assay should be performed after the exposure, and then again at 8–12 weeks after exposure. If either of these tests were to be positive, treatment with isoniazid plus vitamin B_6 for 9 months should be completed to ensure infectious TB disease does not develop [195].

While the USA has about 10,000 TB cases per year, it is important to keep in mind that one third of the world's population is infected with TB, and in 2014, 9.6 million people around the world had TB disease [207].

Varicella or Herpes Zoster

Vulnerable populations to a varicella zoster exposure include people older than 12 months of age who are unimmunized or immunocompromised children without evidence of immunity. Individuals who have contraindications for vaccination

including pregnant women, immunocompromised people, and children less than 12 months of age are recommended to receive varicella zoster IG. Maximum benefit is achieved when PEP is administered as soon as possible after exposure, but may be effective if administered up to 10 days after exposure. Finally, in the absence of availability of IG and contraindications to vaccination, some experts recommend prophylaxis with acyclovir beginning 7–10 days after exposure (administered four times per day for 7 days) [208].

- The varicella vaccine should be administered within 3–5 days of exposure, with a second dose given at the appropriate age interval [198].
- For children under 13 years of age, the minimum interval between doses is 3 months, while for people greater than 13 years of age the minimum interval is 4 weeks [208].

Conclusion

Vaccines represent a large-scale, highly successful public health program that saves lives, reduces morbidity, and saves money. Multiple vaccine types designed to target a substantial variety of pathogens have been developed through rigorous scientific study and research. Vaccination schedules in infancy, childhood, and adulthood are safe and effective in protecting the most vulnerable populations from disease. Diseases once common and devastating in the USA have had substantial decreases in incidence, morbidity, and mortality with the initiation of routine vaccination programs. Worldwide eradication of several vaccine-targeted diseases appears possible. Ongoing research continues to look at improved vaccine efficacy, the longevity of vaccine protection, and special populations requiring enhanced disease protection.

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