Chapter 1
History of Infectious Diseases and Vaccines in Society: Introduction

Pamela G. Rockwell

The success or failure of any government in the final analysis must be measured by the well-being of its citizens. Nothing can be more important to a state than its public health; the state's paramount concern should be the health of its people.

Franklin Delano Roosevelt [2]

Introduction

Franklin D. Roosevelt, as governor of New York (serving from 1929 to 1932) in a report to the New York State Health Commission in 1932 [2], knew that public health was important to society as evidenced by the first line of the report quoted above. His commitment to public health and disease prevention helped incorporate vaccines into US medical practice and pave the way for eradication of polio in the United States. As the 32nd president of the United States (serving from 1933 to 1945), he founded the National Foundation for Infantile Paralysis (NFIP) in 1938, later renamed the March of Dimes. Among many other notable accomplishments, NFIP sponsored a large poliomyelitis vaccine field trial directed by Thomas Francis, Jr., MD in 1954 [3], of the University of Michigan Vaccine Evaluation Center to test the safety and efficacy of the Salk polio vaccine. It was the first wide-scale testing of a vaccine, using 65,000 children volunteered by their parents, to receive either vaccine or placebo injections [4]. Thanks to the polio trial and subsequent vaccine trials, ongoing scientific research, and scholarly activity, we can now prevent more

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infectious diseases through immunizations than ever before. In the medical communities' common goal to cure disease and treat the effects of disease as it occurs, immunizations have been hailed as one of the most effective methods of all medical and public health initiatives to save lives by way of preventing disease [5].

Infectious disease outbreaks have had devastating effects on people and populations, influencing human social and political history throughout recorded time. Hippocrates (460–377 BCE), who was among the first to record his theories on the occurrence of disease, coined the terms *endemic* and *epidemic disease*. He defined endemic diseases as diseases that were always present in a population. Conversely, epidemic diseases were not always invariably present but occurred sometimes in large numbers [6]. Civilizations and their cultures have been shaped, altered, and decimated by disease endemics and epidemics. Outbreaks of disease have been documented since 541 AD in Asia. Though the evidence for epidemics in the non-Western world and in the New World before significant contact with Europeans is scant, we can theorize that infectious diseases have been present around the world as long as man has been present [7]. Cholera, yellow fever, malaria, and plague were constant concerns in the West and in US port cities in the early twentieth century when quarantine was the principle tool of prevention [6]. Through a combination of public health initiatives including improved sanitation and introduction of vaccines, deaths declined markedly in the United States during the twentieth century. This is significantly evidenced by the sharp drop in infant and child mortality and a 29.2-year increase in life expectancy noted during that time [8]. The three leading causes of death in 1900 were pneumonia, tuberculosis (TB), diarrhea, and enteritis, which when combined with diphtheria, caused 1/3 of all deaths. Young children aged fewer than 5 years accounted for 40% of the deaths caused by the forenamed diseases and made up roughly 1/3 of all deaths from all causes. By 1997, that percentage dropped to 1.4% [9, 10] (Fig. 1.1).

The positive effects of vaccines have been documented since the late 1700s when inoculation (introduction of smallpox pustules into the skin) was practiced. Centers for Disease Control and Prevention (CDC) describes the reduction in morbidity and mortality associated with vaccine-preventable diseases in the United States as one of the ten greatest public health achievements of the first decade of the twenty-first century [11]. Despite the success of vaccination, common infectious diseases continue to confer significant societal and individual harm. For example, influenza, a common and familiar infectious disease known as "the flu," is responsible for much morbidity and mortality in the United States. CDC estimates that each year, an average of 226,000 people are hospitalized due to influenza and between 3000 and 49,000 people (mostly adults) die of influenza and its complications, depending on the year and severity of outbreaks. Other infectious diseases also result in significant morbidity and mortality: of the 32,000 cases of invasive pneumococcal disease in adults in 2012, there were approximately 3300 deaths. A total of 800,000–1.4 million people suffer from chronic hepatitis B, with complications such as liver cancer, and in the United States, human papillomavirus (HPV) causes about 17,000 cancers in women and about 9000 cancers in men each year; about 4000 women die each year from cervical cancer [12].

In addition to illness and death, cost to society from infectious diseases can be measured in terms of dollars spent in treating and preventing diseases. The economic analysis of vaccine-preventable disease (VPD) requires examination beyond

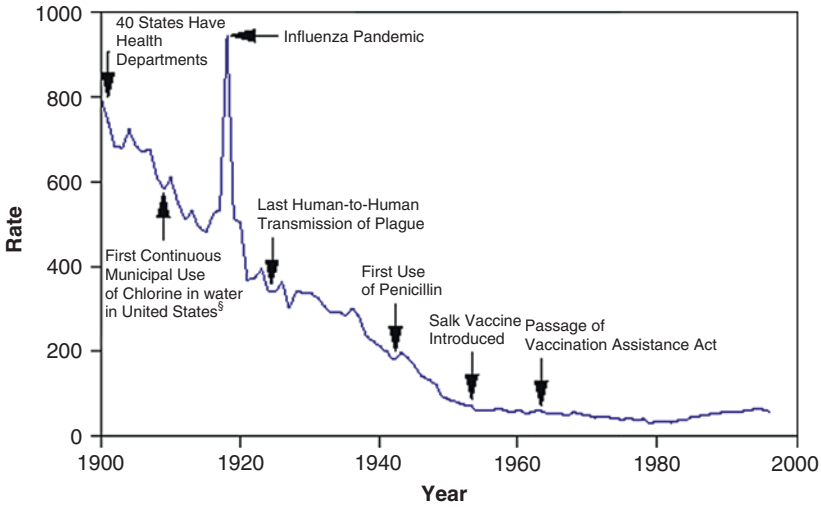


Fig. 1.1 Crude death rate (per 100,000 population per year) for infectious diseases – United States, 1900–1996 (Adapted from Armstrong et al. [8]). §American Water Works Association. Water chlorination principles and practices: AWWA manual M20. Denver, Colorado: American Water Works Association, 1973

the costs of individual illness to account for the costs of protecting society. For example, the 2004 direct cost to the public health infrastructure in Iowa containing one case of measles brought to the United States from an unvaccinated college student who had traveled to India was estimated at $142,452. This is far greater than the estimated cost of uncomplicated individual illness (fewer than $100) [13]. A 2014 report by CDC concluded that routine childhood vaccinations given to infants and young children over the previous two decades will prevent 322 million cases of disease, 21 million hospitalizations, and about 732,000 early deaths over the course of the lifetimes of children born during 1994–2013, for a net societal cost savings of $1.38 trillion which includes $295 billion in direct costs such as medical expenses [14]. Moreover, these calculations may underestimate the full impact of vaccines because only the 14 routine early childhood immunizations that are typically required for school entry were considered, leaving out flu shots and adolescent vaccines along with all the societal benefits those vaccines bestow [12].

Vaccination has led to a dramatic decline in the number of US cases of many infectious diseases. However, unvaccinated American children and adults are susceptible to diseases that are now rare stateside but may be imported into the United States from foreign travelers. Furthermore, those who are unvaccinated are susceptible to exposure to the same infectious diseases while traveling abroad as illustrated by the measles-infected college student returning from travel to India. Additionally, outbreaks of preventable diseases occur when many parents decide not to vaccinate their children, especially when living in a closed community. Pockets of unvaccinated children not only create risk for those unvaccinated children in the community, but also create risk for others outside the community unable to be vaccinated: children too young to be vaccinated and people with weakened immune systems [15].

Around the world, a much larger proportion of children are now protected against a broader range of infectious diseases through vaccinations, but there is still much room for improvement in vaccination rates. VPDs are still responsible for about 25% of the 10 million deaths occurring annually among children under 5 years of age [16]. Mortality estimates are helpful in prioritizing public health intervention, and in the case of VPDs, these estimates indicate the number of deaths that could be averted if existing vaccines were used to their fullest potential.

Take the example of measles again, a highly contagious infectious disease caused by a paramyxovirus with classic symptoms of fever, cough, coryza, conjunctivitis, Koplik spots, and rash, which in 1912 became a nationally notifiable disease in the United States. In the first decade of reporting, an average 6000 measles-related deaths were reported annually. Nearly every child got measles by the time they turned 15; an estimated 3–4 million people were infected each year in the United States, with 48,000 hospitalizations, 4000 cases of encephalitis, and ~400–500 deaths [17]. In the 4 years prior to the US licensure of the measles vaccine in 1963, an average of 503,282 measles cases and 432 measles-associated deaths were reported each year [18]. As the US public eradication of measles effort began, an ambitious Public Health Service statement in 1966 maintained that by the "effective use of [these] vaccines during the coming winter and spring should insure the eradication of measles from the United States in 1967" [19]. Though not eradicated as predicted, by 1998 measles reached a provisional record low number of 89 cases with no measles-associated deaths [20]. All cases in 1998 were either documented to be associated with international importations (69 cases) or believed to be associated with international importations [9]. Over the next decade around the globe, there was also a reduction in measles mortality from an estimated 750,000 deaths in 2000 down to 197,000 in 2007 [21, 22]. Worldwide, measles vaccination prevented an estimated 17.1 million deaths during 2000–2014 [23] (Fig. 1.2).

Infectious Disease: Its Effects on Culture and Populations

Significant Plagues, Pandemics, and Epidemics

Both in ancient times and in the modern day, infectious disease complications range from, at best, a patient forced out of commission for weeks due to illness to far more serious complications such as hearing and vision loss, disfigurement, limb paralysis, limb amputations, seizures, and death. On a much larger scale than individual complications, disease epidemics have decimated entire populations and changed cultures. It wasn't until the 1960s that historian William H. McNeill started producing scholarly writings on history in a completely novel way: he chronicled how infectious disease outbreaks have influenced history. He described how disease has molded many culture's demographics, politics, and ecological resources. His scholarly contributions are the first to correlate historical events and outcomes with disease epidemics [24].

McNeill and other historians since wrote of the Antonine Plague of 165–180 AD, the first major plague known to have influenced culture and civilization. It is reported

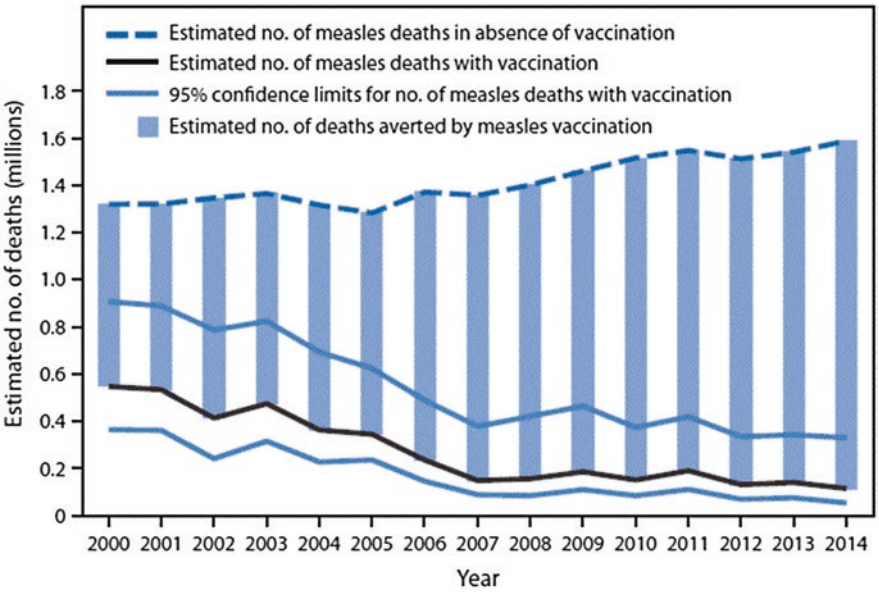


Fig. 1.2 Estimated number of measles deaths and number of averted by measles vaccination – worldwide, 2000–2014 (from citation progress toward regional measles elimination – worldwide 2000–2014 http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6444a4.htm)

to have killed a quarter to a third of Rome's population [25]. Most historians agree that in 165 AD Roman soldiers returning home from war in Mesopotamia caused the plague by introducing what historians believe to be smallpox (never before seen in Europe) to Rome. Rome's two emperors Lucius Verus and Marcus Aurelius Antoninus died from the plague, giving the plague its name. Unfortunately, little record keeping of the plague disease and description of its physical and clinical effects on the sufferer exists. Though the Greek physician, Galen, recorded his observations and a description of the epidemic, his descriptions were scant and he did not give many specific details of the disease. He described the plague as "great" and of long duration and mentioned fever, diarrhea, pharyngitis, as well as a skin eruption, sometimes dry and sometimes pustular appearing on the ninth day of illness, fitting the theory that the plague was caused by smallpox (there is no actual proof of this). The majority of scholars agree that the impact of the plague was severe, affecting ancient Roman traditions and not only influencing spirituality and religion but also influencing military conscription and agricultural and urban economy and depleting the finances of the land. Artistic expression of the time depicted the renewal of spirituality and religiousness. Scholars conclude that the plague and its sequelae created the conditions for the spread of monotheistic religions, such as Mithraism and Christianity [25]. The Antonine Plague, wrote McNeill, coincided with the start of the Roman Empire's 300-year decline [24].

Several hundred years later, in 541 AD, the first of three other historically significant plague pandemics caused by the bacterium *Yersinia pestis* began, these more

carefully recorded than the Antonine Plague. The *Justinian Plague* or *Bubonic Plague*, named after the sixth Byzantine Emperor Justinian I, is characterized by sudden onset fever, headache, chills, and weakness and one or more swollen, tender, and painful lymph nodes (called buboes) and is reported to have killed millions. Numerous references in art, literature, and monuments attest to the horrors and devastation that accompanied the disease. It depopulated many European cities and depressed birth rates for generations, contributing to the fall of Rome. *Yersinia pestis* infects small rodents like rats, mice, and squirrels, and it is usually transmitted to humans through the bite of an infected flea or by handling an animal infected with plague. It was spread across the world by the globalization of rats: black rats brought over from Africa as part of the grain trade to Europe. Over the next 200 years, there were several outbreaks of the Justinian Bubonic Plague which were ultimately responsible for killing over 25 million people and affecting all the Mediterranean basin [26].

The second large pandemic, rising to epidemic proportions in the fourteenth century during the Middle Ages, originated in China several hundred years later, in 1334. This plague was known as the *Black Plague*, or the *Great Plague*. The name was derived by descriptions of people ill with the plague, covered in black boils that oozed blood and pus. At that time, China was one of the busiest trading nations, allowing the plague to spread along the great trade routes to Constantinople and then to Europe where it again devastated Europe, killing nearly 50 million people, an estimated 60% of the European population. The pandemic died down in winter, when fleas went dormant, and flourished in the spring. Even after the worst of each pandemic flair was over, smaller outbreaks continued for centuries, and the disease did not disappear until the 1600s. The devastation of the Black Plague caused massive labor shortages due to high mortality rates, which in turn is credited in speeding up the development of many economic, social, and technical modernizations [27], and has been considered a factor of the onset of the Renaissance in the late fourteenth century (Fig. 1.3).

The "third great plague," the *Modern Plague*, began in the Yunnan province in China in 1855 and appeared in Hong Kong by 1894. In the following 20 years, it spread to port cities around the world via rats on steamships, causing approximately 10 million deaths. It spread from the Yunnan province to all inhabited continents, ultimately killing more than 12 million people in India and China alone [28]. The *Yersinia pestis* bacterium was originally spread by infectious flea bites from infected rats, but it then spread to local populations of ground squirrels and other small mammals. This bubonic plague was endemic in populations of infected ground rodents in central Asia and was a known cause of death among migrant and established human populations in that region for centuries. Increased globalization resulting in more heterogeneous societies led to the dissemination of bubonic plague which still exists in various parts of the world. In 2003, more than 2100 human cases and 180 deaths were recorded by the World Health Organization (WHO), nearly all of them in Africa. The last reported serious outbreak was in 2006 in the Democratic Republic of the Congo in Central Africa, when at least 50 people died. The United States, China, India, Vietnam, and Mongolia are among the other countries that have confirmed human plague cases in recent years. New research suggests Black Death is lying dormant [29].

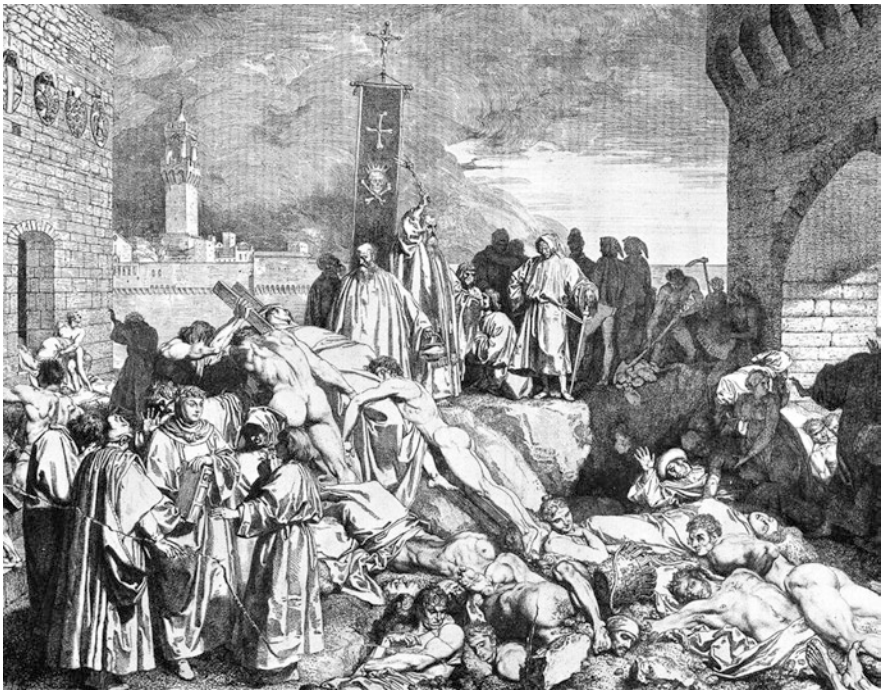


Fig. 1.3 Black plague – engraving taken from the book *Paris Through the Centuries*, *Tome1* (1878) (Photo courtesy of Alamy Images)

The Americas were mostly shielded by geography from the many infectious diseases endemic to Europe and Asia before the sixteenth century. Native Americans had no exposure and thus no immunity to many infectious diseases. The first large-scale contacts between Europeans and native people of the American continents brought overwhelming pandemic of measles and smallpox to the Native Americans in the sixteenth century. These diseases spread rapidly and were lethal, leading to a drastic drop in the Native American population. The Aztec and Inca civilizations in Central and South America were crippled [30], and much of Native American cultures collapsed.

The Path to Vaccine Discovery

Smallpox: From Early Recorded Man to the Twenty-First Century

To review the history of modern vaccines, one must start with a brief review of the history of smallpox, an exanthematous DNA viral disease. The deadliest form of smallpox is caused by the variola major virus and is without a known cure. It can be

contracted via airborne particles or through direct contact with infected bodily fluids or contaminated objects such as bedding or clothing. There is no animal reservoir of smallpox and no human carriers – the virus has to spread continually from human to human to survive [31]. Smallpox is believed to have appeared at the time of the first agricultural settlements in northeastern Africa around 10,000 BCE. The earliest physical evidence of smallpox is the pustular rash on the mummified body of Pharaoh Ramesses V of Egypt, who died in 1157 BCE [32]. Population effects of the disease can be traced from China in 1122 BCE and on to Europe between the fifth and sixth centuries. Although epidemics of disease are described in the Bible and in Greek and Roman literature, descriptions of clinical signs are sparse [33]. One of the epidemics that can be identified with some certainty as smallpox occurred in Athens beginning in 430 BCE and was described by Thucydides, a Greek historian, born 460 BCE [31]. Later, during the fourteenth-century Middle Ages, smallpox was frequently endemic (along with other diseases like typhoid, measles, dysentery, and the plague), resulting in the fall of the Native American civilizations in the 1500s due to the introduction of smallpox by Spanish and Portuguese conquistadors to the New World.

Smallpox first appeared in England in the sixteenth century. A particularly virulent strain emerged in the early seventeenth century, and by the eighteenth century, smallpox was endemic: it killed one tenth of the population of British India, one tenth of all Swedish infants, one seventh of all Russian infants, and over 400,000 Europeans each year [34].

After several decades of endemicity, smallpox became almost wholly a disease of childhood with a high mortality rate. It resulted in a death rate of roughly 25–30% and one third of smallpox survivors were reported to have gone blind. It was common knowledge that survivors of smallpox became immune to the disease, and almost all adults were immune to smallpox, having survived the disease as children [35]. Outbreaks of variola major occurred until the end of the nineteenth century. Man's attempt to prevent smallpox initially through inoculation (also known as variolation) was the first known attempt to minimize or prevent disease.

Variolation and Inoculation: Earliest Forms of Vaccination

The terms *inoculation* from the Latin *inoculare*, meaning "to graft," and *variolation* were often used interchangeably. Variolation specifically refers to the deliberate exposure of a person to smallpox from pustules or scabs of a person with smallpox. The Chinese are generally given credit for variolation. Textual evidence such as Zhang Lu-yu's *Zhangshi Yitong* (Zhang's Medical Compendium) from 1695 offers a description of smallpox inoculation through variolation involving nasal insufflation of dried finely powdered human pox crusts taken from a patient in the recovery stages of smallpox [36]. During this same period in India, scarification procedures were invented either separately or imported from China [37]. From there, the practice of cutaneous variolation passed to the Middle East and Africa, from Turkey to Great Britain, then to the rest of Europe and elsewhere [38].

Inoculation through variolation was introduced in England in the early 1700s [39]. The smallpox virus was introduced subcutaneously via a lancet with fresh matter taken from a ripe pustule of someone suffering from smallpox. This technique carried the risk of death to the patient inoculated and also potentially infected others around the patient as the inoculated patient became infectious. However, the risk of death from inoculation was much less than the risk of death from contracting the disease outright, and vaccination through inoculation was recommended by many. Mathematically minded doctors and scientists calculated the risks of dying from inoculation – roughly 1 in 100 in the 1720s – and compared it to the risk of dying from smallpox, about 1 in 7 [40]. There were those who recommended universal inoculation like Daniel Bernoulli, a Swiss mathematician who wrote a mathematical analysis in 1760 and calculated that approximately three quarters of all living people during that time had been infected with smallpox. He argued through mathematical equations that many lives would be saved if smallpox were completely eliminated, and he encouraged universal inoculation against smallpox [35].

Edward Jenner

In 1757 a young boy by the name of Edward Jenner was inoculated with smallpox in Gloucester England and thus became immune to the disease [41]. By 1798, the young Edward Jenner had become Dr. Edward Jenner, known for developing a procedure to inoculate people with fresh cowpox lesions, conferring immunity to smallpox. Cowpox is an infectious disease caused by the cowpox virus, a zoonotic virus that can be transferred between animals and man. The transfer of the disease was observed in dairymaids who touched the udders of infected cows and who consequently developed pustules on their hands and forearms. These dairymaids were noted to have immunity to smallpox with later exposures. Jenner was the first to keep scientific records that documented that cowpox inoculation conferred immunity to those later exposed to smallpox. Through his work of inoculation with cowpox, the word *vaccination* was derived: *vacca*, Latin for cow, and *vaccina*, Latin for vaccinia virus of the genus *Orthopoxvirus* [42].

To be historically fair, prior to the work of Jenner, other country physicians and farmers in the dairy lands of eighteenth-century England and physicians and farmers in other parts of the world the previous century knew of and practiced inoculation. Recognition is due to Benjamin Jesty, a farmer in Yetminster, England, who, in an attempt to protect his family in 1774 (24 years before Jenner's experiments), used material from udders of cattle that he knew had cowpox and transferred the material with a small lancet to the arms of his wife and two young boys, ages two and three [43]. So sure of his vaccination success, Benjamin Jesty years later purposefully had one of his son's exposed to known case of smallpox, proving his son's immunity [44]. Despite his successful inoculation of his family, Jesty was said to be ridiculed by the town folk of Yetminster. Much of society at that time was not yet

Fig. 1.4 Edward Jenner, vaccinating his young child, held by Mrs. Jenner; a maid rolls up her sleeve, a man stands outside holding a cow. Colored engraving by C. Manigaud after E Hamman. The Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PE Credit: Wellcome Library, London. *Image*: *Wellcome Images L0011550*

ready for change by way of scientific interventions. In rural areas, people were often superstitious and the last execution for witchcraft had taken place only 62 years before. Word spread of what Jesty had done to his family, and he and they became the object of their neighbors' scorn and derision. Eventually Jesty moved out of Yetminster to another part of England, and records show that he went on to successfully inoculate many others over the years [45].

However, no one before Jenner had documented or recorded any scientific investigation or study on the matter of inoculation. Jenner recorded and published his findings. Vaccines have been associated with clinical trials ever since: within 5 years of his publication, doctors in Europe and North America conducted trials both in hospitals and in communities to test the safety and efficacy of cowpox vaccine. These trials set the model for evaluations of subsequent vaccines [46]. Therefore, Jenner can be thought of as one of the first physicians to promote and practice evidenced-based medicine (Fig. 1.4).

Closer to Home: Smallpox in Eighteenth-Century Americas and the American Revolution

The early history of the United States of America is profoundly influenced by the effects of smallpox. The conflict between Great Britain and 13 of its North American colonies (self-named the United States of America) which had declared themselves independent was unduly influenced by smallpox. Outbreaks of smallpox nearly cost the Americans the Revolutionary War (1775–1783). The American Revolutionaries were fighting both the British and disease [47] as most of the British troops were immune to smallpox, either from inoculation, or from having had the disease, and the majority of the Revolutionaries were not. Furthermore, the British commanders offered voluntary inoculation to its army members not already immune to the disease, while the American commanders initially did not. Few people in North America from the 13 colonies, including the fighting troops, had been exposed to smallpox prior to the war. Quarantine was the initial American line of defense against smallpox: all incoming vessels that had smallpox on board during their voyage, or that came from a place where smallpox was known to be prevalent, were required to undergo an examination by doctors or Boston selectmen. The selectmen quarantined anyone with obvious disease or who had been known to come from an area with smallpox.

Inoculation was not new to the Americas, but it was not widely practiced. Prior to the American Revolution, sporadic inoculation had begun during a 1721 smallpox epidemic in Boston. Cotton Mather, a Puritan divine and scientist, had successfully inoculated 242 persons with good results: only four of those inoculated died from the procedure [48]. Though the risk of death due to inoculation was much less than the risk of death due to natural disease, the people of Boston did not condone inoculation for both religious and financial reasons. Many physicians and clergymen in Boston accused Mather of mocking God's will by interfering with the course of a plague. They argued that Mather subjugated a high cost to society through inoculation, determined by labor time lost to those who needed 1–2 months to recover from the effects of the inoculation. Furthermore, the risk of transmitting smallpox from those inoculated to others in the community who were not inoculated was a threat Boston society was not ready to accept. Legislative action was taken and every colony except Pennsylvania passed laws to restrict the practice of inoculation [33].

Fortunately, one very important American had been exposed to smallpox as an adolescent and survived with immunity. George Washington, the Commander in Chief of the Continental Army, who later served as the first US president (serving 1789–1797) was immune to smallpox. His immunity ultimately helped shape the course of the Revolutionary War. Washington, born in Virginia, had contracted smallpox as an adolescent during a visit to Barbados in November 1751 when he and his older brother were sent there by their parents in hopes that the warm climate would help his bother recuperate from tuberculosis – it did not.

As commander in chief during the American Revolution, Washington realized how contagious smallpox was and what a devastating effect it could have on his troops and battle outcomes. He strategically used immune troops for certain military maneuvers that resulted in close engagement with the British. Initially he declined to inoculate his troops for the same reasons many people of the American colonies professed: inoculation was dangerous with its small risk of death to those inoculated, and inoculation of large numbers of troops would render the troops ineffective for 1–2 months while they recuperated from the procedure. He instead chose to rely on quarantine measures to contain outbreaks of smallpox – until the Battle of Quebec. After the disastrous loss at Quebec in 1775–1776, reportedly largely due to smallpox infection among his troops, he changed his mind and decided to inoculate his troops. In speaking about smallpox, he stated:

> I know that it is more destructive to an army in the natural way than the sword. [47]

On February 5, 1777, Washington ordered the inoculation of all susceptible troops in the Continental camp and of every new recruit. This was the first time an American force had been immunized by command order. The Continental Army became the first in the world to have an organized program for smallpox prevention. It signaled the first of many vaccination programs US military troops would undertake. To prevent smallpox from spreading via secondary contact with inoculated troops, Washington had the procedure performed in "inoculation hospitals" and isolated the troops in vaccination huts [49]. For more than a year, the Army provided free compulsory inoculation for all soldiers [50]. Washington reportedly kept his inoculation actions secret to prevent the British from discovering the majority of his troops were temporarily incapacitated. By the end of the war, the Continental Army was virtually as immune as the British. Washington's decision to inoculate had evened the odds in the war. Some argue that had he decided to inoculate his army sooner, US land acquisition after the Revolutionary War would have been different: more of what is now Canada would belong to the United States [51].

Since the Revolutionary War, the US military has promoted vaccination of its troops and has been actively engaged in vaccine research [50]. The US Army Medical Research Institute of Infectious Diseases (USAMRIID) created in 1969 spearheads research to develop medical solutions: vaccines, drugs, diagnostics, and information to protect military service members from biological threats. USAMRIDD works alongside CDC and the World Health Organization (WHO) and collaborates with industry and federal agencies including the Department of Health and Human Services and the Department of Homeland Security, playing a critical role in the status of our country's preparedness for biological terrorism and biological warfare [52].

Smallpox Today

Before 1972, smallpox vaccination was recommended for all US children at 1 year of age, and most states required evidence of vaccination for school entry. Vaccination was also required for military recruits and tourists visiting other countries. Due to

these vaccination efforts, the last natural outbreak of smallpox occurred in 1949. Routine vaccination of Americans stopped in 1972 after the disease was declared eradicated in the United States [53]. Eight years later, naturally occurring smallpox was declared eradicated from the planet thanks to a global campaign that began in 1967 under the auspices of the WHO. On May 8, 1980, the World Health Assembly announced that the world was free of smallpox and recommended that all countries cease vaccination:

"The world and all its people have won freedom from smallpox, which was the most devastating disease sweeping in epidemic form through many countries since earliest times, leaving death, blindness and disfigurement in its wake."

In 1986 the WHO proposed that all laboratories destroy their variola stocks or transfer them to one of the two WHO reference labs: the Institute of Virus Preparations in Moscow, Russia, or the CDC in Atlanta, Georgia. All countries reported compliance. Until recently, the US government provided the vaccine only to a few hundred scientists and medical professionals working with smallpox and similar viruses in a research setting. From 1983 through 2002, most service members did not get vaccinated against smallpox, but in December 2002, President George W. Bush announced that smallpox vaccination was restarted for all service members and government personnel in high-risk areas, and he set an example and received the vaccine himself on December 2, 2002. Between December 2002 and May 2014, more than 2.4 million service members received smallpox vaccinations [54].

Germ, or biological warfare, is described as the deliberate use of a microorganism or toxin as a weapon. A category "**A**" organism is defined as an organism/biological agent that is easy to disseminate and transmit from person to person, one that poses the highest risk to national security and public health. Smallpox was involved in what many describe as biological warfare during the 1700s. Some historians believe that roughly 20 years before the American Revolutionary War, during the French-Indian War (1754–1767), Sir Jeffrey Amherst, the commander of the British forces in North America, suggested the deliberate use of smallpox to diminish the Native Indian population hostile to the British through dissemination of pox-infested blankets to the Native Indians [55]. Today, it is reported that, beginning in 1980, the Soviet government embarked on a program to produce the smallpox virus in large quantities and adapt it for use in weapons [56]. After the anthrax terrorist attacks in September and October 2001 when powdered anthrax spores were mailed through the US postal system, preparedness for additional bioterrorist threats led the federal government to implement a smallpox vaccination program for civilian public health responders that reached nearly 40,000 workers [57]. An updated smallpox response plan was released, and the federal government has called on all states to devise comprehensive mass prophylaxis plans to ensure that civilian populations have timely access to necessary antibiotics and/or vaccines in the event of future outbreaks of infectious diseases. The government has enough vaccine stock to vaccinate every person in the United States in the event of a smallpox emergency [53]. The deliberate release of smallpox as a biological weapon today would be an international crime of unprecedented proportions – one case of smallpox would be considered an emergency.

Dryvax, the smallpox vaccine originally licensed in 1944 to Wyeth Laboratories, Inc., of Madison, N.J., was manufactured until the mid-1980s when the WHO declared that smallpox had been eradicated. Currently there is one licensed smallpox vaccine, ACAM2000, licensed on August 31, 2007, manufactured by Sanofi Pasteur Biologics Co. of Cambridge, MA, based on the same strain of virus as Dryvax. ACAM2000 is indicated for active immunization against smallpox disease for persons determined to be at high risk for smallpox infection. ACAM2000 is administered by scarification to the deltoid muscle or the posterior aspect of the arm over the triceps muscle. On May 2, 2005, the Center for Biologics Evaluation and Research (CBER), a division of the US Federal Food and Drug Administration (FDA), licensed Vaccinia Immune Globulin Intravenous (VIGIV) manufactured by Cangene Corporation of Winnipeg, Manitoba, Canada. VIGIV is used to treat rare serious complications of smallpox vaccination [58].

Development of the Germ Theory and Early Modern Vaccines

The development of the germ theory is an important step in the development of vaccines as we know them today. Louis Pasteur (1822–1895), a French scientist known for his discovery of pasteurization, developed the first laboratory vaccine and was the first to propose the "germ theory" of disease: that diseases are caused by microorganisms. He theorized that vaccination could be applied to any microbial disease. He discovered and documented methods relating to the virulence of microbes and how they could be attenuated so that live microbes could be used to make *prophylactic vaccines*. Additionally, he introduced the concept of *therapeutic vaccines* with his studies of rabies, demonstrating what we now call post-infection prophylaxis [59]. One interesting story involves Pasteur's earliest vaccine research involving chickens. Pasteur received a strain of bacteria that caused chicken cholera from Henry Toussaint, a professor of the Veterinary School of Toulouse. Pasteur learned how to grow the chicken cholera microbe in chicken broth and experimented first by feeding chickens food contaminated with a culture of chicken cholera microbes. This resulted in death for most of the chickens. Pasteur recorded his experiments: he learned that the chickens that survived were then resistant to a second exposure of the same pathogen given by an inoculation of a lethal dose of the chicken cholera microbe. He determined that those chickens had immunity against chicken cholera.

A fortuitous accident occurred when Pasteur went on vacation and his assistant forgot to continue the experiment. The bacterial inoculation cultures Pasteur meant for inoculation of the experimental chickens were left in a medium that was exposed to room air for about a month. Later, when the experiment resumed and the chickens were injected with the now unintentionally "attenuated" strains of bacteria, the chickens did not die but only contracted a mild form of the disease. When Pasteur later reinjected these chickens with lethally-dosed, fresh, purulent bacteria, they did not get ill: Pasteur had successfully vaccinated the chickens against cholera using an attenuated vaccine [60]!

Pasteur also developed another attenuated vaccine in his laboratory against anthrax. In 1881, his vaccine experiments proved vaccine-induced immunity to anthrax in animals. He gave his live, attenuated anthrax vaccine to some animals in his experiment but not all. He then proved that when later exposed to anthrax, all vaccinated animals survived while his control group died [61]. In addition, Louis Pasteur was also instrumental in documenting post-infection prophylaxis, also known as postexposure prevention (PEP), through vaccines. PEP refers to a preventive medical treatment that is started immediately after exposure to a pathogen to prevent infection and development of disease caused by the pathogen. PEP is commonly and effectively used to prevent the outbreak of rabies after a bite from or contact with a rabid animal or prevent tetanus after a potential exposure to tetanus. Pasteur first developed a vaccine against rabies in livestock in 1884, then proved its effectiveness in post-infection prophylaxis in humans in 1885 by successfully vaccinating Joseph Meister, a 9-year-old boy who was bitten several times by a rabid dog. The boy survived and did not contract rabies [62].

History of Modern Vaccines Late Nineteenth and Twentieth Centuries

Types of Vaccines

There are several different types of vaccines in use today and some currently in development.

Toxoids

When a toxin produced by a bacterial pathogen is the main cause of illness, toxoid vaccines may be effective to prevent those toxin-producing diseases. Toxoids are inactivated forms of bacterial toxins, or "detoxified" toxins, used for the purpose of immunization. They cannot cause the disease they prevent and there is no possibility of reversion to virulence [63]. When the immune system receives a vaccine containing a harmless toxoid, it learns how to fight off the natural toxin by producing antibodies that lock onto and block the toxin [41, 64]. Diphtheria and tetanus are two examples of toxoid vaccines.

Live, Attenuated Vaccines

Live, attenuated vaccines contain a version of the living microbe that has been weakened and unable to cause disease. They elicit strong cellular and antibody responses and often confer lifelong immunity with one or two doses [64]. Smallpox, yellow fever, and MMR vaccines are examples of these.

Inactivated Vaccines

Inactivated vaccines are produced by killing the disease-causing microbe with chemicals, heat, or radiation. These are more stable and safer than live vaccines; they do not require refrigeration and can be easily stored and transported in a freeze-dried form. However, these stimulate a weaker immune system response than live vaccines, often requiring booster shots [64]. Hepatitis A, rabies, and injectable polio vaccines are examples of these.

Subunit/Conjugate Vaccines

Subunit vaccines include only the antigens of a microbe that best stimulate the immune system to protect against it and do not contain live components of the pathogen. Conjugate vaccines are a special type of subunit vaccines, made to create immunity to the outer coating of polysaccharides that many bacteria have so that the immature immune systems of infants and younger children can recognize and respond to them. The hepatitis B, influenza, and Hib vaccines are examples of a subunit conjugate vaccines [64].

DNA Vaccines

DNA vaccines are still in experimental stages and developing rapidly. They involve the direct introduction into appropriate tissues of a plasmid contacting the DNA sequence encoding the antigen(s) against which an immune response is sought and relies on the in situ production of the target antigen [63–66]. The first DNA vaccines licensed for marketing are likely to use plasmid DNA derived from bacterial cells. Others may use RNA or complexes of nucleic acid molecules. Several types are currently under testing in humans including West Nile and Zika virus vaccines [64–66].

Diseases and Their Vaccines

Diphtheria toxin: diphtheria is a potentially fatal disease caused by the exotoxin produced by the bacterium *Corynebacterium diphtheriae* that primarily affects tissues of the upper respiratory tract and kills its victims slowly by suffocation. Symptoms include a thick, gray membrane covering the throat and tonsils, a sore throat, lymphadenopathy, fever, chills, and nerve damage. In 1884, German physician Edwin Klebs (1834–1913) successfully isolated the bacteria that caused diphtheria. In 1888, French physician, bacteriologist, and immunologist Emile Roux discovered the diphtheria toxin. This discovery, in conjunction with the scientific contributions of others (including Emil Von Behring and Paul Ehrlich), led to the development of the diphtheria vaccine [37].

Tetanus toxin: tetanus is an acute, often fatal disease caused by an exotoxin produced by the bacterium *Clostridium tetani*, which is characterized by generalized rigidity and convulsive spasms of skeletal muscles. The jaw is usually involved (lockjaw) and then the neck before becoming more generalized. Experiments that began in 1884 with animals injected with pus from fatal human tetanus cases eventually led to the neutralization of the toxin. During World War I (WWI), passively transferred antitoxin and passive immunization in humans were used for treatment and prophylaxis. Tetanus toxoid was developed in 1924 and used during WWII [67].

Yellow fever: yellow fever is a highly fatal hemorrhagic infection caused by a small, enveloped, single-stranded RNA virus. Symptoms include fever, chills, loss of appetite, nausea, muscle pain, and headaches. In some people symptoms worsen after 4–5 days and liver damage may occur, causing jaundice (yellow skin), bleeding risk, and kidney damage. Approximately half of those who develop severe symptoms die within 7–10 days. During the Spanish-American War of 1898, yellow fever was a serious problem for US troops. US Army physician Walter Reed headed up the Yellow Fever Commission, which traveled to Cuba and validated a theory presented by Cuban physician Carlos Finlay two decades earlier: mosquitoes were responsible for the spread of the disease. Later it was shown that the underlying cause of yellow fever is a virus that uses mosquitoes as vectors. This discovery led many scientists to work on yellow fever vaccine development until Max Theiler and other Rockefeller Foundation scientists developed a successful live attenuated vaccine for yellow fever in 1937 [68].

Tuberculosis

Tuberculosis was known as *phthisis* and *consumption* from the time of Hippocrates to the eighteenth century and known as the *white death* and the *great white plague* during the nineteenth century. It was an epidemic in Europe during the eighteenth and nineteenth centuries and caused millions of deaths [69].

Robert Koch, known as the founder of modern bacteriology, revealed in 1882 that the causative agent of tuberculosis is *Mycobacterium tuberculosis*, later known as Koch's bacillus. From there came the criteria for proof of bacterial causality. Koch's postulates state: "the organism must be present in diseased tissues; it must be isolated and grown in pure culture; and the cultured organism must induce the disease when inoculated into healthy experimental animals" [70]. Koch's discovery facilitated the development of the tuberculosis vaccine. Bacillus Calmette-Guerin (BCG), a live attenuated vaccination developed in 1924, was first used in newborns and has become the most widely administered of all vaccines in the World Health Organization (WHO) Expanded Program for Immunization. Unfortunately, it is only partially effective, providing some protection against severe forms of pediatric TB, but is not completely protective against disease in infants and is unreliable against adult pulmonary TB [71]. Nearly a century after development, this vaccine is still used today. No universal BCG vaccination policy exists. Some countries merely recommend its use and others have implemented immunization programs. It is not routinely recommended in the United States [72].

Influenza: influenza is a highly contagious disease caused by influenza viruses that infect the respiratory passages causing fever, cough (usually dry), headache, sore throat, runny nose, severe muscle and joint aches, and may result in severe illness and death. It is spread mainly via droplets, which are produced when people infected with flu cough, sneeze, or talk. Prior to 1933, the bacterium *Haemophilus influenzae* was mistakenly thought to cause the flu. The first flu vaccine was developed by Jonas Salk and Thomas Francis to protect US military forces against the flu during WWII. In 1943, a successful controlled trial of the vaccine was conducted on 12,500 men in units of the Army Specialized Training Program at universities and at medical/dental schools in different areas of the United States, proving the first effective influenza virus vaccine [73].

Note: There have been four major flu pandemics recorded throughout history. In 1918–1919 the Spanish flu pandemic was responsible for approximately 50 million deaths worldwide and for nearly 675,000 deaths in the United States. The second flu pandemic in 1957–1958 hit the United States in two waves killing 69,800 people, far fewer people than the 1918 pandemic. The elderly had the highest rates of death during these pandemics. The third pandemic occurred in 1968–1969 from a new influenza virus that originated in Hong Kong. It was the mildest of all the flu pandemics, resulting in 33,800 American deaths. Again, the elderly population was the most likely to die. The 2009–2010 H1N1 swine flu pandemic was declared a public health emergency by the US government on April 26, 2009. H1N1 was reported in mostly young people. There were approximately 60.8 million cases, 274,304 hospitalizations, and 12,469 deaths, which occurred in the United States due to H1N1 during that pandemic. Massive vaccination campaigns led to the vaccination of 80 million people during that time and a decline of flu activity. WHO declared an end to the global H1N1 flu pandemic August, 2010 [74, 75].

Poliomyelitis: polio is an acute paralytic disease caused by three poliovirus serotypes. It is an intestinal infection spread between humans through the fecal-oral route. In the 1950s Jonas Salk and Albert Sabin produced the first polio vaccines; Salk produced a killed-virus injectable vaccine (IPV) and Sabin a live-virus oral vaccine (OPV). The WHO proposed worldwide poliomyelitis eradication in 1988. Unfortunately, this goal is still not met. Sporadic cases of wildtype polio occur in various parts of the developing world in Afghanistan, India, Nigeria, and Pakistan [76, 77]. The last cases of naturally occurring paralytic polio in the United States were in 1979 when an outbreak occurred among the Amish in several Midwestern states [78]. From 1980 to date, there were 162 confirmed cases of paralytic polio reported – of those 162 cases, 8 were acquired outside the United States and imported. The last imported case caused by wild poliovirus into the United States occurred in 1993. The remaining 154 cases were vaccine-associated paralytic polio caused by live oral poliovirus vaccine. OPV has not been used in the United States since 2000 but is still used in many parts of the world. IPV is currently the only vaccine used in the United States against polio [79].

Measles, mumps, and rubella: measles, one of the most contagious infectious diseases known, is caused by an RNA virus. Until 2000, measles was still the leading cause of vaccine-preventable childhood death worldwide [80]. It is still endemic

worldwide, and although declared eliminated from the United States in 2000, sporadic outbreaks still occur. Mumps, also a highly contagious viral illness, causes parotiditis and serious complications like meningitis, encephalitis, deafness, and orchitis which can lead to sterility in men. Rubella (also known as German measles) virus was isolated in the early 1960s and is associated with terrible birth defects if a pregnant woman contracts the disease. Congenital rubella syndrome (CRS) was discovered in the 1940s and is associated with cataracts, deafness, congenital heart disease, encephalitis, mental retardation, pneumonia, hepatitis, thrombocytopenia, metaphyseal defects diabetes mellitus, and thyroiditis.

The MMR vaccine is a mixture of live attenuated viruses of the three diseases. A licensed vaccine to prevent measles was first available in 1963. Live attenuated vaccines for mumps and rubella became available in 1967 and 1969, respectively [81, 82]. An attenuated combination measles-mumps-rubella vaccine was licensed in 1973 by Merck [83] in 2000; measles was declared no longer endemic in the United States in 2005; and CDC announced that rubella was no longer endemic in the United States.

MMR-Autism Hoax

The MMR vaccine is not linked in any way to autism. Perhaps one of the biggest medical hoaxes in this century is the one perpetrated by Dr. Thomas Wakefield, a British gastroenterologist [84] who described such a link in a paper published in the Lancet in 1998 [85]. His paper and the subsequent media explosion around publicizing his false theory eroded parental confidence in vaccinations, government, and public health institutions first in England and later in the United States. After 10 years of controversy and investigation and multiple studies later, Wakefield's assertion of the alleged autism-MMR link was disproved [86]. More than 20 studies found no evidence of connection between receipt of the MMR vaccine and autism disorders, and Britain's General Medical Council (GMC) determined after its hearings that Wakefield was guilty of dishonesty and serious professional misconduct with regard to his MMR-autism research and the publication of his paper [84, 87]. His paper was retracted from the Lancet and his medical license revoked. His later attempts, after moving to Texas, to sue the *British Medical Journal* for libel were dismissed in a Texas court [88]. Many believe the media has given celebrities who comment on an autism-MMR link far more attention than they deserve (Jenny McCarthy and Robert De Niro come to mind), and segments of the public have confused celebrity status with authority [89]. The GMC states that anti-vaccine groups and conspiracy proponents promoting such an association should be ignored [87].

Hepatitis A and B: hepatitis (liver inflammation) with fever, fatigue, abdominal and joint pain, loss of appetite, and jaundice is caused by several different strains of virus, and strains A and B have been isolated and differentiated since the early 1940s. Hepatitis A-inactivated vaccine was licensed in 1995. A plasma-derived hepatitis B vaccine was licensed in 1981, and in 1986 a recombinant hepatitis B vaccine

was licensed. ACIP recommended routine hepatitis B vaccination for all infants in 1991. In 2001 Twinrix, a combined hepatitis A-inactivated and hepatitis B recombinant vaccine was licensed. In 2002 a vaccine combing diphtheria, tetanus, acellular pertussis, inactivated polio, and hepatitis B antigen (Pediarix) was licensed [37].

Haemophilus influenzae type b (Hib): *Haemophilus influenzae* is a bacterial infection spread person-to-person by direct contact or through respiratory droplets that mainly causes illness in babies and young children. Infections range from ear infections to pneumonia, septic arthritis, epiglottitis, meningitis, and sepsis.

Hib vaccine: in 1985 Hib vaccine was recommended routinely for children at 4 months of age and for children at 15 months of age enrolled in child care facilities. By 1988 the recommendation changed to vaccinate all children at 18 months of age. By 1990 the age for vaccine recommendation was lowered to 15 months of age for all children, and in 1991 the recommendation changed to vaccinate all children beginning at 2 months of age. In the United States between 1980 and 1990, the incidence of Hib disease was 40–100/100,000 among children under 5 years of age. Since 1990, with routine use of Hib conjugate vaccine, the incidence of invasive Hib disease has decreased to 1.3/100,000 children [90].

Pneumococcus: *Streptococcus pneumoniae* bacteria, referred to as pneumococcus, cause many types of illnesses ranging from ear/sinus infections and pneumonia to sepsis and meningitis and occur in all ages from infancy to geriatric years. Pneumonia is the most common serious form of pneumococcal disease. Two enhanced pneumococcal polysaccharide vaccines were licensed in 1983 (Pneumovax 23 and Pnu-Immune 23), covering 23 purified capsular polysaccharide antigens of *Streptococcus pneumoniae* and replacing the 1977 pneumococcal vaccine covering 14 serotypes of pneumococcal [37]. Pneumococcal 7-valent Conjugate Vaccine (Prevnar) was approved by the FDA in 2000 for immunization of infants and toddlers [91], and Pneumococcal 13-valent Conjugate Vaccine (PCV13) approved in 2010 for use in place of Prevnar expanded to broader use in all adults age 19–64 with certain underlying medical conditions and all adults over age 65 in 2014 [92].

Varicella zoster: varicella (chickenpox) and herpes zoster (shingles) are caused by the varicella zoster virus. Chickenpox, typically a relatively mild childhood illness with fever, malaise, headache, abdominal pain, and a characteristic pruritic exanthem, follows initial exposure to the virus. Shingles is a painful dermatomal rash resulting from reactivation of the dormant virus and is often followed by pain in the distribution of the rash (post-herpetic neuralgia). The varicella zoster vaccine is the first and only licensed live, attenuated herpesvirus vaccine in the world. Varivax was licensed in 1995. In 2006, VariZIG, an immune globulin product for postexposure prophylaxis of varicella, became available. Also in 2006, the FDA licensed Zostavax, approved for use in people aged 50 years of age and older to prevent shingles and ACIP recommended for those over 60 years old [37].

Rotavirus: rotavirus is the leading cause of severe acute gastroenteritis in young infants and children worldwide, transmitted primarily by the fecal-oral route, both through close person-to-person contact and through fomites. The virus is highly contagious. Millions to billions of viral particles can be present within one gram of diarrheal stool. In 2008, rotavirus caused an estimated 453,000 deaths worldwide in

children younger than 5 years of age. Prior to the vaccine, almost all US infants were infected with rotavirus before their fifth birthday. The original live, oral vaccine was introduced in 1999 but was pulled off the market in the United States 14 months later due to several reported cases of vaccine-associated intussusception. Two different vaccines are currently licensed for infants in the United States (RotaTeq and Rotarix), both having gone through rigorous clinical trials to prove their safety [93].

Meningococcus: meningococcal disease can refer to any disease caused by *Neisseria meningitidis* bacteria, an aerobic, gram-negative diplococcus that colonizes the human nasopharynx and is transmitted by respiratory tract droplets. Invasive disease may cause sepsis and meningitis and death. Sudden fever, headache, and stiff neck are typical symptoms along with nausea, vomiting, light sensitivity, rash, and confusion. Risk factors include crowding such as seen in military recruits or college students living in dormitories, tobacco smoke exposure, and alcohol-related behaviors. Persons who acquire the organism in the nasopharynx may develop a carrier state, but only a few develop invasive disease. The carrier state is common in college students. The overall case-fatality rate for invasive disease in the United States is 10–15%, even with appropriate antibiotics. Quadrivalent meningococcal vaccines protect against serogroups A, C, W, and Y and recommended to all children at ages 11–12 and 16 years and meningococcal serogroup B vaccine for those children at high risk and as a permissive recommendation for others [90].

Human papillomavirus (HPV): HPV is the most common sexually transmitted infection, and transmission occurs most frequently with sexual intercourse but can occur also with non-penetrative intimate contact. An estimated 14 million new infections occur per year, and an estimated 79 million persons are currently infected in the United States. HPV types 6 and 11 cause at least 90% of genital warts, and types 16 and 18 cause 70% of cervical cancers and 70% of genital cancers. Cancers of the penis, vagina, vulva, anus, rectum, and nasopharyngeal head and neck structures are caused by HPV. The first HPV vaccine was licensed in the United States in 2006. The nine-valent (9vHPV) vaccine (covering serotypes 6, 11, 16, 18, 31, 33, 45, 52, 58) is indicated for all adolescents ages 11–12 in a two-dose series, 6–12 months apart. For those who start the vaccination series between 15–26 years of age, a three-dose series is required for effective immune response [90].

Creation of the World Health Organization Global Recommendations for Vaccines

During the twentieth century, several international organizations devoted to health and welfare were created, but only a few survived post WWII. One group that persisted after the war, the Health Organization of the League of Nations (started in 1920), had been the weekly distributor of epidemiological information, using both

Geneva and a special bureau in Singapore as collecting posts. This health organization helped create an international public health system and expanded existing international epidemic control systems. Global disease management became more scientific, more technical, and less political under it than disease management was prior to WWII. The Health Organization of the League of Nations represented the beginning of social medicine, public health separation from politics, and global public health reform [94]. Eventually the United Nations (UN) proposed that even greater international organizational work and guidance was needed to combat the many diseases affecting people worldwide. The *World Health Organization* was proposed as a matter of international concern for "economic, social, cultural, educational, health and related matter" during the UN conference held in San Francisco, April 1945. One year later, an outline for the proposed constitution of the organization was proposed in 1946, but it wasn't until April 7, 1948, that all 26 signatures from all 26 member countries were obtained, officially documenting WHO's beginning [95].

The principle advisory group to the WHO for vaccines and immunization is the Strategic Advisory Group of Experts on Immunization (SAGE), established by the Director-General of the WHO in 1999. SAGE is charged with advising on overall global policies and strategies concerning all vaccine-preventable diseases. In 2005, the 58th World Health Assembly along with the United Nations Children's Emergency Fund (UNICEF) introduced the Global Immunization Vision and Strategy 2006–2015 (GIVS) as a framework for strengthening national immunization programs. SAGE was restructured to meet the needs of GIVS, reporting to the WHO Director-General, responsible for reviewing and approving all WHO policy recommendations, including the WHO position papers on vaccines. GIVS' goal was to reduce mortality due to vaccine-preventable diseases by two-thirds by 2015 compared to 2000 levels, equal to more than 40 million lives saved [16, 96]. There are four key objectives to achieve this goal:

1. To immunize more people against more diseases
2. To introduce a range of newly available vaccines and technologies
3. To integrate other critical health interventions with immunization
4. To manage vaccination programs within the context of global interdependence [96]

At the time of this publication, outcome data for GIVS is not yet available.

Beginnings of CDC

Centers for Disease Control and Prevention was established on July 1, 1946 in Atlanta, Georgia by Dr. Joseph W. Mountin of the US Public Health Services' Bureau of State Services. It was then called Communicable Disease Center (CDC). CDC had grown out of an organization called the Malaria Control in War Areas (MCWA), which had been established in 1942 to control malaria around military

training bases in the United States. Initially CDC focused on MCWA's interests: fighting malaria, typhus, and other infectious diseases of concern post WWII. It had a three-fold primary mission: field investigation, training, and control of communicable diseases. Over the next 60 years, CDC's title changed several times (The National Communicable Disease Center, Center for Disease Control, Centers for Disease Control) to its name today, Centers for Disease Control and Prevention. Throughout its title changes, the initials "CDC" have remained the same [97]. Over time, under the leadership of chief epidemiologist Dr. Alexander Langmuir from 1949 to 1970, CDC's role in the United States grew dramatically, becoming a large federal agency. Today CDC helps to control epidemics within the United States. CDC tracks diseases and provides expert scientific advice on health issues to policy makers, serving as a reference laboratory to the states and informing the public about health issues through the *Morbidity and Mortality Weekly Report* (MMWR). Epidemiologists from CDC routinely assist state health departments in investigating and controlling outbreaks of infectious and noninfectious disease. On a larger scale, it has grown to provide leadership, often in partnership with the WHO in controlling emerging infectious disease worldwide [6].

Vaccine Recommendations in the United States

Today, all vaccine recommendations for American children and adults are made by CDC's Advisory Committee on Immunization Practices (ACIP) using evidence-based decision-making with input from many organizations and experts. Prior to the 1960s, this was not the case. In 1961, the main body making recommendations on vaccine use in the United States was the American Academy of Pediatrics' Committee on Infectious Diseases (COID) [98]. COID vaccine recommendations were first published in 1938 in a pamphlet with a red cover, giving rise to the publication's official nickname "Red Book." Red Book continues to be a major resource both for physicians and for government committees such as ACIP [99]. For children of the early 1960s, no formal nationwide immunization program existed. Vaccines were administered in private practices and local health departments and paid for out of pocket or provided by using state or local government funds with some support from federal Maternal and Child Health Block Grant funds. In 1962, the Vaccination Assistance Act (Section 317 of the Public Health Service Act) was passed to "achieve as quickly as possible the protection of the population, especially of all preschool children . . . through intensive immunization activity over a limited period of time. . ." The initial intention was to allow CDC to support mass, intensive vaccination campaigns. In addition, the Vaccination Assistance Act established a mechanism to provide ongoing financial support to state or local health departments and direct support "in lieu of cash." The direct support included provision of vaccines and of CDC public health advisors to assist in managing the programs. Section 317 has been reauthorized repeatedly since 1962 and remains one of the most important

means of supporting health department immunization activities with federal funds [57]. At the initiation of the 317 funding program in 1963, there were few vaccines to consider. There were only three vaccines routinely recommended for children including diphtheria, tetanus, pertussis (DTP), oral polio (OPV), and smallpox. The measles vaccine was to be licensed later that year.

Vaccine recommendations until 1964 did not formally involve the federal government. The federal government involvement occurred through convening ad hoc expert advisory groups to address individual issues. One such issue was the adverse effect of paralysis related to poorly manufactured vaccines during the field trial of Jonas Salk's inactivated polio vaccine (IPV). Federal ad hoc groups were also formed to provide advice about the influenza pandemic of 1957, Albert Sabin's attenuated oral polio vaccine (OPV), and the measles vaccines prior to release. The frequency and complexity of issues requiring discussion and opinion statements from the federal government led CDC to propose an ongoing Advisory Committee on Immunization Practices. ACIP was established in 1964 and served as a technical advisory committee to the Public Health Service. It was initially comprised of eight members, including the CDC Director, who served as Chair [100, 101]. ACIP directed its recommendations to public health agencies.

Today, ACIP includes 15 voting members selected by the Secretary of the US Department of Health and Human Services and makes recommendations to CDC's director. Voting members are selected via an application and nomination process and serve voluntarily. Fourteen of the members have expertise in vaccinology, virology, immunology, pediatrics, internal medicine, family medicine, nursing, public health, infectious diseases, and/or preventive medicine. One member is a consumer representative to provide perspectives on the social and community aspects of vaccination. In addition, there are eight ex officio members who represent other federal agencies with immunization programs and 30 nonvoting representatives of liaison organizations. ACIP recommendations have major impact on immunization policies and practice in the United States as well as other countries. The committee meets three times a year in Atlanta at CDC, where it makes recommendations on how to use vaccines and related agents that are licensed by the US Food and Drug Administration (FDA) to control disease in the United States. These recommendations are then forwarded to CDC's director for approval, and once approved, they are published in CDC's MMWR. When data is available, specific rules of evidence, such as those followed by the US Preventive Services Task Force (USPSTF), are used to judge the quality of data and make decisions regarding the nature and strength of recommendations. ACIP recommendations on 17 vaccine-preventable diseases are published in the MMWR, the *Pink Book* (*Epidemiology and Prevention of Vaccine-Preventable Diseases*), the AAP *Red Book*, and in the US immunization schedules for children, adolescents, and adults. MMWR publication represents the final and official CDC recommendations for immunization of the US population [102].

Development of the Vaccines for Children Program

In 1993, a Childhood Immunization Initiative began with the goal of achieving, by 1996, 90% immunization coverage among preschool-aged children for vaccines recommended during the first 2 years of life. A critical part of the Childhood Immunization Initiative was to eliminate financial barriers to vaccination and ensure children could be vaccinated at their site of usual care (medical home). The vaccines for children (VFC) program was established through the Omnibus Reconciliation Act of 1993, as an entitlement program for vaccines recommended by ACIP. The program includes children who are Medicaid eligible, completely uninsured, or Native American Indian/Alaska Native. Those children, whose insurance does not cover vaccinations or who are underinsured, can receive vaccines at Federally Qualified Health Centers [103]. Coverage has grown to include approximately 45% of US children, including about 70% of African-American and Hispanic children. VFC authorizes ACIP to decide which vaccines will be covered [104].

The Childhood Immunization Initiative is also responsible for the development of the National Immunization Survey (NIS) in 1994, a program for documentation of vaccinations. Through random-digit dialing surveys, statistically valid immunization coverage rates for all 50 states and several urban areas were tracked. This helped improve progress toward meeting national immunization goals and identified problem areas requiring special interventions. The NIS documented in 1996 $\geq$ 90% coverage for the following vaccines routinely recommended for preschool-aged children: DTP (three or more doses), polio (three or more doses), MMR (one dose), and *Haemophilus influenzae* type b (Hib b) (three or more doses). The 70% coverage goal of three or more doses of hepatitis B vaccine was also met. NIS illustrated that racial and ethnic disparities in immunization rates, once as high as 20 percentage points for measles, had substantially narrowed [104]. To continue to ensure high coverage rates for immunizations for all ages, health plans today are required by law to cover recommended preventive services without charging a deductible, copayment, or coinsurance. This requirement is stipulated by the Affordable Care Act passed by Congress and signed into law by President Obama on March 23, 2010.

Up from a handful of vaccine recommendations for eight vaccine-preventable diseases in the 1980s, (Fig. 1.5) [105] today children in the United States receive vaccines to prevent 16 diseases (Table 1.1). Most diseases targeted by these vaccines have declined to historically low levels (Table 1.2) [106]. Familiar to most today, the current annual childhood schedule as endorsed by ACIP, AAP, and AAFP has been available since 1995. The annual updates since contain detailed information about the recommended vaccines, including specific age- and dosage-related information, catch-up schedules, and information about new vaccines as they are added to the schedule [107]. They can be found at https://www.cdc.gov/vaccines/schedules/.

TABLE 2. Recommended schedule for active immunization of normal infants and children*

Recommended age†	Vaccine(s)§	Comments
2 mos	DTP#1¶, OPV#1**	OPV and DTP can be given earlier in areas of high endemicity
4 mos	DTP#2, OPV#2	6-wk to 2-mo interval desired between OPV doses
6 mos	DTP#3	An additional dose of OPV at this time is optional in areas with a high risk of poliovirus exposure
15 mos††	MMR§§, DTP#4, OPV#3	Completion of primary series of DTP and OPV
18 mos	HbCV¶¶	Conjugate preferred over polysaccharide vaccine***
4–6 yrs	DTP#5†††, OPV#4	At or before school entry
14–16 yrs	Td§§§	Repeat every 10 yrs throughout life

*See Table 3 for the recommended immunization schedules for infants and children up to their seventh birthday not immunized at the recommended times.
†These recommended ages should not be construed as absolute, e.g., 2 months can be 6–10 weeks. However, MMR should not be given to children <12 months of age. If exposure to measles disease is considered likely, then children 6 through 11 months old may be immunized with single-antigen measles vaccine. These children should be reimmunized with MMR when they are approximately 15 months of age.
‡For all products used, consult the manufacturers' package enclosures for instructions regarding storage, handling, dosage, and administration. Immunobiologics prepared by different manufacturers can vary, and those of the same manufacturer can change from time to time. The package inserts are useful references for specific products, but they may not always be consistent with current ACIP and American Academy of Pediatrics immunization schedules.
§DTP = Diphtheria and Tetanus Toxoids and Pertussis Vaccine, Adsorbed. DTP may be used up to the seventh birthday. The first dose can be given at 6 weeks of age and the second and third doses given 4–8 weeks after the preceding dose.
**OPV = Poliovirus Vaccine Live Oral, Trivalent: contains poliovirus types 1, 2, and 3.
††Provided at least 6 months have elapsed since DTP#3 or, if fewer than 3 doses of DTP have been received, at least 6 weeks since the last previous dose of DTP or OPV. MMR vaccine should not be delayed to allow simultaneous administration with DTP and OPV. Administering MMR at 15 months and DTP#4 and OPV#3 at 18 months continues to be an acceptable alternative.
§§MMR = Measles, Mumps, and Rubella Virus Vaccine, Live. Counties that report ≥5 cases of measles among preschool children during each of the last 5 years should implement a routine 2-dose measles vaccination schedule for preschoolers. The first dose should be administered at 9 months or the first health-care contact thereafter. Infants vaccinated before their first birthday should receive a second dose at about 15 months of age. Single-antigen measles vaccine should be used for children aged <1 year and MMR for children vaccinated on or after their first birthday. If resources do not allow a routine 2-dose schedule, an acceptable alternative is to lower the routine age for MMR vaccination to 12 months.
¶¶HbCV = Vaccine composed of Haemophilus influenzae b polysaccharide antigen conjugated to a protein carrier. Children <5 years of age previously vaccinated with polysaccharide vaccine between the ages of 18 and 23 months should be revaccinated with a single dose of conjugate vaccine if at least 2 months have elapsed since the receipt of the polysaccharide vaccine.
***If HbCV is not available, an acceptable alternative is to give Haemophilus influenzae b polysaccharide vaccine (HbPV) at age ≥24 months. Children at high risk for *Haemophilus influenzae* type b disease where conjugate vaccine is not available may be vaccinated with HbPV at 18 months of age and revaccinated at 24 months.
†††Up to the seventh birthday.

1989 childhood immunization schedule

Fig. 1.5 1989 Recommendations (From: http://www.cdc.gov/vaccines/schedules/images/schedule1989s.jpg)

ACIP began publishing an annual adult schedule in 1984 [108] for those aged 19 years and older and is now developed with approval from the American College of Physicians (ACP), the AAFP, the American College of Obstetricians and Gynecologists (ACOG), and the American College of Nurse-Midwives (ACNM). There is one adult schedule organized by vaccine and age group and another schedule organized by medical and other indications. These schedules may be found at: http://www.cdc.gov/vaccines/schedules/hcp/adult.html.

Since their inception, immunization schedules have become more complicated (Fig. 1.6) and detailed, with separate catch-up schedules (Fig. 1.7) just as complex.

Table 1.1 Year of US licensure of selected childhood vaccines

Vaccine	Year of first US licensure
Tetanus toxoid	1943
Trivalent inactivated influenza	1945
Tetanus and diphtheria toxoids	1953 for children aged >7 years.; 1970 for children aged <7 years
Inactivated polio	1955
Oral polio	1963
Diphtheria-tetanus-pertussis	1970
Diphtheria-tetanus-acellular pertussis	1991
Measles-mumps-rubella	1963 (measles); 1967 (mumps); 1969 (rubella); 1971 (measles, mumps, rubella combined)
Hepatitis B	1981 (plasma derived); 1986 (recombinant)
Haemophilus influenzae type b conjugate	1987 for children aged ≥18 months; 1990 for infants
Hepatitis A	1995
Varicella	1995
Pneumococcal conjugate	2000 (7-valent); 2010 (13-valent)
Live attenuated influenza	2003
Tetanus-diphtheria-acellular pertussis	2005
Meningococcal conjugate	2006
Rotavirus	2006
Human papillomavirus	2006

Source: USIS (1967–1985); NHIS (1991–1993); CDC, NCHS, and NIS (1994–2009); CDC, NIP, and NCHS; no data during 1986–1990 due to cancelation of USIS because of budget reductions
Note: Children in the USIS and NHIS were 24–35 months of age. Children in the NIS were 19–35 months of age
https://www.cdc.gov/mmwr/preview/mmwrhtml/su6004a9.htm
Abbreviations: *MMR* measles-mumps-rubella, *DTP/DTaP* diphtheria and tetanus and acellular pertussis, *Hib Haemophilus influenzae* type b, *Heb B* hepatitis B, *PCV7* 7-valent pneumococcal conjugate vaccine, *USIS* US Immunization Survey, *NHIS* National Health Interview Survey, *NIS* National Immunization Survey, *NCHS* National Center for Health Statistics, *NIP* National Immunization Program, *NCIRD* National Center for Immunization and Respiratory Diseases
[a]DTP(3+) is not a Healthy People 2010 objective. DTaP(4) is used to assess Healthy People 2010 objectives

Schedules are color-coded for ease in interpretation. The comparison of the 1989 immunization recommendations highlighted in Fig. 1.5 in contrast to the 2017 recommendations illustrated in Fig. 1.6 epitomizes the incredible progress and increased complexity in vaccine science developing in just over 25 years. The necessary footnotes, determined with evidenced-based rigor, which give further guidance on the use of the recommended vaccines, now take up three full pages of small-type text (Fig. 1.8a, b, c, d) [105].

Table 1.2 Comparison of annual morbidity from vaccine-preventable diseases during the twentieth century and 2009

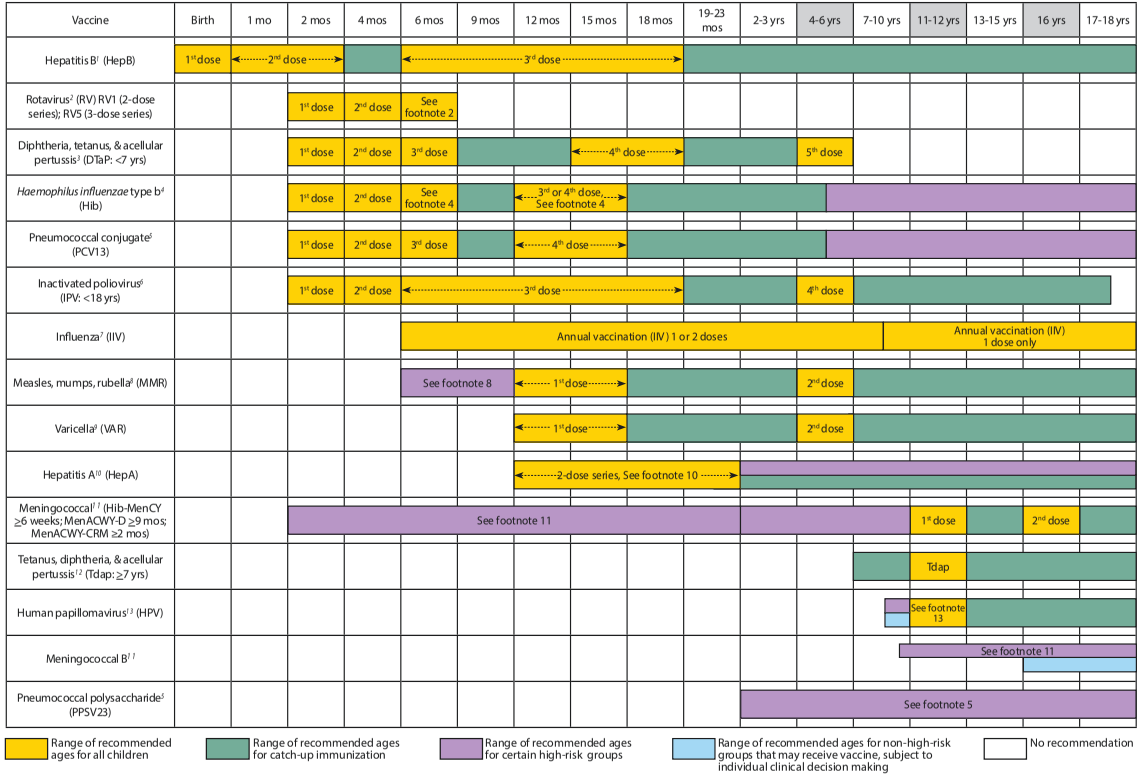
Disease	Twentieth century[a]	2010[c]	% Reduction
Diphtheria	21,053	0	100
Hepatitis A	117,333	8493[d]	93
Hepatitis B, acute	66,232	9419[d]	86
Haemophilus influenzae type b in children aged <5 years	20,000	240[e]	99
Measles	530,217	63	>99
Mumps	162,344	2612	98
Pertussis	200,752	27,538	86
Pneumococcus, invasive			
All ages	63,607	44,000[f]	30
<5 years	16,069	4700[f]	72
Poliomyelitis, paralytic	16,316	0	100
Rotavirus, hospitalizations	62,500[b]	28,125[d]	55
Rubella	47,745	5	>99
Congenital rubella syndrome	152	0	100
Smallpox	29,005	0	100
Tetanus	580	26	96
Varicella	4,085,120	408,572[d]	90

[a]Estimated annual average number of cases in the prevaccine era for each disease. Source: JAMA 2007;298:2155–63
[b]Source: MMWR 2009;58(No. RR-2)
[c]Source: MMWR 2011; 60(32):1088–1101
[d]2009 estimate
[e]23 type b and 223 unknown serotype (among children <5 years of age)
[f]Source: http://www.cdc.gov/abcs/reports-findings/survreports/spneu09.html
From: https://www.cdc.gov/mmwr/preview/mmwrhtml/su6004a9.htm

Summary

Morbidity and mortality conferred by infectious diseases have had devastating effects on the lives of people and populations, influencing social and political history throughout recorded time. Through modern medicine and technology, we can now prevent more infectious disease through immunizations than ever before. Vaccines save direct and indirect costs such as medical expenses to society and work days missed, with projected savings in the trillions of dollars in addition to over 700,000 lives saved in the United States for children born between 1995 and 2013 [14]. A historical review of infectious diseases in society, including the great pandemics and epidemics from 300 BCE through the early eighteenth century, helps highlight how infectious disease affects lives, civilizations, and culture. Smallpox

Figure 1. Recommended Immunization Schedule for Children and Adolescents Aged 18 Years or Younger—United States, 2017.
(FOR THOSE WHO FALL BEHIND OR START LATE, SEE THE CATCH-UP SCHEDULE [FIGURE 2]).
These recommendations must be read with the footnotes that follow. For those who fall behind or start late, provide catch-up vaccination at the earliest opportunity as indicated by the green bars in Figure 1. To determine minimum intervals between doses, see the catch-up schedule (Figure 2). School entry and adolescent vaccine age groups are shaded in gray.



NOTE: The above recommendations must be read along with the footnotes of this schedule.

Fig. 1.6 Childhood immunization schedule (from: https://www.cdc.gov/vaccines/schedules/downloads/child/0-18yrs-child-combined-schedule.pdf)

FIGURE 2. Catch-up immunization schedule for persons aged 4 months through 18 years who start late or who are more than 1 month behind—United States, 2017.

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

Vaccine	Minimum Age for Dose 1	Minimum Interval Between Doses			
		Dose 1 to Dose 2	Dose 2 to Dose 3	Dose 3 to Dose 4	Dose 4 to Dose 5
Children age 4 months through 6 years					
Hepatitis B[7]	Birth	4 weeks	8 weeks *and* at least 16 weeks after first dose. Minimum age for the final dose is 24 weeks.		
Rotavirus[2]	6 weeks	4 weeks	4 weeks[2]		
Diphtheria, tetanus, and acellular pertussis[3]	6 weeks	4 weeks	4 weeks	6 months	6 months[3]
Haemophilus influenzae type b[4]	6 weeks	4 weeks if first dose was administered before the 1st birthday. 8 weeks (as final dose) if first dose was administered at age 12 through 14 months. No further doses needed if first dose was administered at age 15 months or older.	4 weeks[4] if current age is younger than 12 months **and** first dose was administered at younger than age 7 months, **and** at least 1 previous dose was PRP-T (ActHib, Pentacel, Hiberix) or unknown. 8 weeks *and* age 12 through 59 months (as final dose)[4] • if current age is younger than 12 months **and** first dose was administered at age 7 through 11 months; OR • if current age is 12 through 59 months **and** first dose was administered before the 1st birthday, **and** second dose administered at younger than 15 months; OR • if both doses were PRP-OMP (PedvaxHIB; Comvax) **and** were administered before the 1st birthday. No further doses needed if previous dose was administered at age 15 months or older.	8 weeks (as final dose) This dose only necessary for children age 12 through 59 months who received 3 doses before the 1st birthday.	
Pneumococcal[5]	6 weeks	4 weeks if first dose administered before the 1st birthday. 8 weeks (as final dose for healthy children) if first dose was administered at the 1st birthday or after. No further doses needed for healthy children if first dose was administered at age 24 months or older.	4 weeks if current age is younger than 12 months and previous dose given at <7 months old. 8 weeks (as final dose for healthy children) if previous dose given between 7-11 months (wait until at least 12 months old); OR if current age is 12 months or older and at least 1 dose was given before age 12 months. No further doses needed for healthy children if previous dose administered at age 24 months or older.	8 weeks (as final dose) This dose only necessary for children aged 12 through 59 months who received 3 doses before age 12 months or for children at high risk who received 3 doses at any age.	
Inactivated poliovirus[6]	6 weeks	4 weeks[6]	4 weeks[6]	6 months[6] (minimum age 4 years for final dose).	
Measles, mumps, rubella[8]	12 months	4 weeks			
Varicella[9]	12 months	3 months			
Hepatitis A[10]	12 months	6 months			
Meningococcal[11] (Hib-MenCY ≥6 weeks; MenACWY-D ≥9 mos; MenACWY-CRM ≥2 mos)	6 weeks	8 weeks[11]	See footnote 11	See footnote 11	
Children and adolescents age 7 through 18 years					
Meningococcal[11] (MenACWY-D ≥9 mos; MenACWY-CRM ≥2 mos)	Not Applicable (N/A)	8 weeks[11]			
Tetanus, diphtheria; tetanus, diphtheria, and acellular pertussis[12]	7 years[12]	4 weeks	4 weeks if first dose of DTaP/DT was administered before the 1st birthday. 6 months (as final dose) if first dose of DTaP/DT or Tdap/Td was administered at or after the 1st birthday.	6 months if first dose of DTaP/DT was administered before the 1st birthday.	
Human papillomavirus[13]	9 years	Routine dosing intervals are recommended.[13]			
Hepatitis A[10]	N/A	6 months			
Hepatitis B[7]	N/A	4 weeks	8 weeks **and** at least 16 weeks after first dose.		
Inactivated poliovirus[6]	N/A	4 weeks	4 weeks[6]	6 months[6]	
Measles, mumps, rubella[8]	N/A	4 weeks			
Varicella[9]	N/A	3 months if younger than age 13 years. 4 weeks if age 13 years or older.			

NOTE: The above recommendations must be read along with the footnotes of this schedule.

Fig. 1.7 Catch-up schedule (from: https://www.cdc.gov/vaccines/schedules/downloads/child/0-18yrs-child-combined-schedule.pdf)

a **Footnotes — Recommended Immunization Schedule for Children and Adolescents Aged 18 Years or Younger, UNITED STATES, 2017**

For further guidance on the use of the vaccines mentioned below, see: www.cdc.gov/vaccines/hcp/acip-recs/index.html.
For vaccine recommendations for persons 19 years of age and older, see the Adult Immunization Schedule.

Additional information

- For information on contraindications and precautions for the use of a vaccine and for additional information regarding that vaccine, vaccination providers should consult the ACIP General Recommendations on Immunization and the relevant ACIP statement, available online at www.cdc.gov/vaccines/hcp/acip-recs/index.html.
- For purposes of calculating intervals between doses, 4 weeks = 28 days. Intervals of 4 months or greater are determined by calendar months.
- Vaccine doses administered ≤4 days before the minimum interval are considered valid. Doses of any vaccine administered ≥5 days earlier than the minimum interval or minimum age should not be counted as valid doses and should be repeated as age-appropriate. The repeat dose should be spaced after the invalid dose by the recommended minimum interval. For further details, see Table 1, *Recommended and minimum ages and intervals between vaccine doses, in MMWR, General Recommendations on Immunization and Reports / Vol. 60 / No. 2*,available online at www.cdc.gov/mmwr/pdf/rr/rr6002.pdf.
- Information on travel vaccine requirements and recommendations is available at wwwnc.cdc.gov/travel/.
- For vaccination of persons with primary and secondary immunodeficiencies, see Table 13, *Vaccination of persons with primary and secondary immunodeficiencies*, in *General Recommendations on Immunization* (ACIP), available at www.cdc.gov/mmwr/pdf/rr/rr6002.pdf.; and Immunization in Special Clinical Circumstances, (American Academy of Pediatrics). In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2015 report of the Committee on Infectious Diseases. 30th ed.* Elk Grove Village, IL: American Academy of Pediatrics, 2015:68-107.
- The National Vaccine Injury Compensation Program (VICP) is a no-fault alternative to the traditional legal system for resolving vaccine injury petitions. Created by the National Childhood Vaccine Injury Act of 1986, it provides compensation to people found to be injured by certain vaccines. All vaccines within the recommended childhood immunization schedule are covered by VICP except for pneumococcal polysaccharide vaccine (PPSV23). For more information; see www.hrsa.gov/vaccinecompensation/index.html.

1. **Hepatitis B (HepB) vaccine. (Minimum age: birth)**
Routine vaccination:
At birth:
   - Administer monovalent HepB vaccine to all newborns within 24 hours of birth.
   - For infants born to hepatitis B surface antigen (HBsAg)-positive mothers, administer HepB vaccine and 0.5 mL of hepatitis B immune globulin (HBIG) within 12 hours of birth. These infants should be tested for HBsAg and antibody to HBsAg (anti-HBs) at age 9 through 12 months (preferably at the next well-child visit) or 1 to 2 months after completion of the HepB series if the series was delayed.
   - If mother's HBsAg status is unknown, within 12 hours of birth, administer HepB vaccine regardless of birth weight. For infants weighing less than 2,000 grams, administer HBIG in addition to HepB vaccine within 12 hours of birth. Determine mother's HBsAg status as soon as possible and, if mother is HBsAg-positive, also administer HBIG to infants weighing 2,000 grams or more as soon as possible, but no later than age 7 days.

   Doses following the birth dose:
   - The second dose should be administered at age 1 or 2 months. Monovalent HepB vaccine should be used for doses administered before age 6 weeks.
   - Infants who did not receive a birth dose should receive 3 doses of a HepB-containing vaccine on a schedule of 0, 1 to 2 months, and 6 months, starting as soon as feasible (see figure 2).
   - Administer the second dose 1 to 2 months after the first dose (minimum interval of 4 weeks); administer the third dose at least 8 weeks after the second dose AND at least 16 weeks after the **first** dose. The final (third or fourth) dose in the HepB vaccine series should be administered **no earlier than age 24 weeks**.
   - Administration of a total of 4 doses of HepB vaccine is permitted when a combination vaccine containing HepB is administered after the birth dose.

   Catch-up vaccination:
   - Unvaccinated persons should complete a 3-dose series.
   - A 2-dose series (doses separated by at least 4 months) of adult formulation Recombivax HB is licensed for use in children aged 11 through 15 years.
   - For other catch-up guidance, see Figure 2.
2. **Rotavirus (RV) vaccines. (Minimum age: 6 weeks for both RV 1 [Rotarix] and RV5 [RotaTeq])**
Routine vaccination:
Administer a series of RV vaccine to all infants as follows:
   1. If Rotarix is used, administer a 2-dose series at ages 2 and 4 months.
   2. If RotaTeq is used, administer a 3-dose series at ages 2, 4, and 6 months.
   3. If any dose in the series was RotaTeq or vaccine product is unknown for any dose in the series, a total of 3 doses of RV vaccine should be administered.

   Catch-up vaccination:
   - The maximum age for the first dose in the series is 14 weeks, 6 days; vaccination should not be initiated for infants aged 15 weeks, 0 days, or older.
   - The maximum age for the final dose in the series is 8 months, 0 days.
   - For other catch-up guidance, see Figure 2.
3. **Diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine. (Minimum age: 6 weeks. Exception: DTaP-IPV [Kinrix, Quadracel]: 4 years)**
Routine vaccination:
   - Administer a 5-dose series of DTaP vaccine at ages 2, 4, 6, 15 through 18 months, and 4 through 6 years. The fourth dose may be administered as early as age 12 months, provided at least 6 months have elapsed since the third dose.
   - Inadvertent administration of fourth DTaP dose early: If the fourth dose of DTaP was administered at least 4 months after the third dose of DTaP and the child was 12 months of age or older, it does not need to be repeated.

   Catch-up vaccination:
   - The fifth dose of DTaP vaccine is not necessary if the fourth dose was administered at age 4 years or older.
   - For other catch-up guidance, see Figure 2.
4. ***Haemophilus influenzae* type b (Hib) conjugate vaccine. (Minimum age: 6 weeks for PRP-T [ActHIB, DTaP-IPV/Hib (Pentacel), Hiberix, and Hib-MenCY (MenHibrix)], PRP-OMP [PedvaxHIB])**
Routine vaccination:
   - Administer a 2- or 3-dose Hib vaccine primary series and a booster dose (dose 3 or 4, depending on vaccine used in primary series) at age 12 through 15 months to complete a full Hib vaccine series.
   - The primary series with ActHIB, MenHibrix, Hiberix, or Pentacel consists of 3 doses and should be administered at ages 2, 4, and 6 months. The primary series with PedvaxHIB consists of 2 doses and should be administered at ages 2 and 4 months; a dose at age 6 months is not indicated.
   - One booster dose (dose 3 or 4, depending on vaccine used in primary series) of any Hib vaccine should be administered at age 12 through 15 months.
   - For recommendations on the use of MenHibrix in patients at increased risk for meningococcal disease, refer to the meningococcal vaccine footnotes and also to *MMWR* February 28, 2014 / 63(RR01):1-13, available at www.cdc.gov/mmwr/PDF/rr/rr6301.pdf.

Fig. 1.8 (**a–d**) Footnotes to childhood immunization schedule (Fig. 1.6) and catch-up schedule (Fig. 1.7) (from: https://www.cdc.gov/vaccines/schedules/downloads/child/0-18yrs-child-combined-schedule.pdf)

b For further guidance on the use of the vaccines mentioned below, see: www.cdc.gov/vaccines/hcp/acip-recs/index.html.

Catch-up vaccination:

- If dose 1 was administered at ages 12 through 14 months, administer a second (final) dose at least 8 weeks after dose 1, regardless of Hib vaccine used in the primary series.
- If both doses were PRP-OMP (PedvaxHIB or COMVAX) and were administered before the first birthday, the third (and final) dose should be administered at age 12 through 59 months and at least 8 weeks after the second dose.
- If the first dose was administered at age 7 through 11 months, administer the second dose at least 4 weeks later and a third (and final) dose at age 12 through 15 months or 8 weeks after second dose, whichever is later.
- If first dose is administered before the first birthday and second dose administered at younger than 15 months, a third (and final) dose should be administered 8 weeks later.
- For unvaccinated children aged 15–59 months, administer only 1 dose.
- For other catch-up guidance, see Figure 2. For catch-up guidance related to MenHibrix, see the meningococcal vaccine footnotes and also *MMWR* February 28, 2014 / 63(RR01):1-13, available at www.cdc.gov/mmwr/PDF/rr/rr6301.pdf.

Vaccination of persons with high-risk conditions:

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

- For patients younger than age 5 years undergoing chemotherapy or radiation treatment who received a Hib vaccine dose(s) within 14 days of starting therapy or during therapy, repeat the dose(s) at least 3 months following therapy completion.
- Recipients of hematopoietic stem cell transplant (HSCT) should be revaccinated with a 3-dose regimen of Hib vaccine starting 6 to 12 months after successful transplant, regardless of vaccination history; doses should be administered at least 4 weeks apart.
- A single dose of any Hib-containing vaccine should be administered to unimmunized* children and adolescents 15 months of age and older undergoing an elective splenectomy; if possible, vaccine should be administered at least 14 days before procedure.
- Hib vaccine is not routinely recommended for patients 5 years or older. However, 1 dose of Hib vaccine should be administered to unimmunized* persons aged 5 years or older who have anatomic or functional asplenia (including sickle cell disease) and unimmunized* persons 5 through 18 years of age with HIV infection.

** Patients who have not received a primary series and booster dose or at least 1 dose of Hib vaccine after 14 months of age are considered unimmunized.*

5. **Pneumococcal vaccines. (Minimum age: 6 weeks for PCV13, 2 years for PPSV23)**

Routine vaccination with PCV13:

- Administer a 4-dose series of PCV13 at ages 2, 4, and 6 months and at age 12 through 15 months.

Catch-up vaccination with PCV13:

- Administer 1 dose of PCV13 to all healthy children aged 24 through 59 months who are not completely vaccinated for their age.
- For other catch-up guidance, see Figure 2.

Vaccination of persons with high-risk conditions with PCV13 and PPSV23:

- All recommended PCV13 doses should be administered prior to PPSV23 vaccination if possible.
- For children aged 2 through 5 years with any of the following conditions: chronic heart disease (particularly cyanotic congenital heart disease and cardiac failure); chronic lung disease (including asthma if treated with high-dose oral corticosteroid therapy); diabetes mellitus; cerebrospinal fluid leak; cochlear implant; sickle cell disease and other hemoglobinopathies; anatomic or functional asplenia; HIV infection; chronic renal failure; nephrotic syndrome; diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, and Hodgkin disease; solid organ transplantation; or congenital immunodeficiency:
  1. Administer 1 dose of PCV13 if any incomplete schedule of 3 doses of PCV13 was received previously.
  2. Administer 2 doses of PCV13 at least 8 weeks apart if unvaccinated or any incomplete schedule of fewer than 3 doses of PCV13 was received previously.
  3. The minimum interval between doses of PCV13 is 8 weeks.
  4. For children with no history of PPSV23 vaccination, administer PPSV23 at least 8 weeks after the most recent dose of PCV13.
- For children aged 6 through 18 years who have cerebrospinal fluid leak; cochlear implant; sickle cell disease and other hemoglobinopathies; anatomic or functional asplenia; congenital or acquired immunodeficiencies; HIV infection; chronic renal failure; nephrotic syndrome; diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, and Hodgkin disease; generalized malignancy; solid organ transplantation; or multiple myeloma:
  1. If neither PCV13 nor PPSV23 has been received previously, administer 1 dose of PCV13 now and 1 dose of PPSV23 at least 8 weeks later.
  2. If PCV13 has been received previously but PPSV23 has not, administer 1 dose of PPSV23 at least 8 weeks after the most recent dose of PCV13.
  3. If PPSV23 has been received but PCV13 has not, administer 1 dose of PCV13 at least 8 weeks after the most recent dose of PPSV23.
- For children aged 6 through 18 years with chronic heart disease (particularly cyanotic congenital heart disease and cardiac failure), chronic lung disease (including asthma if treated with high-dose oral corticosteroid therapy), diabetes mellitus, alcoholism, or chronic liver disease, who have not received PPSV23, administer 1 dose of PPSV23. If PCV13 has been received previously, then PPSV23 should be administered at least 8 weeks after any prior PCV13 dose.
- A single revaccination with PPSV23 should be administered 5 years after the first dose to children with sickle cell disease or other hemoglobinopathies; anatomic or functional asplenia; congenital or acquired immunodeficiencies; HIV infection; chronic renal failure; nephrotic syndrome; diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, and Hodgkin disease; generalized malignancy; solid organ transplantation; or multiple myeloma.

6. **Inactivated poliovirus vaccine (IPV). (Minimum age: 6 weeks)**

Routine vaccination:

- Administer a 4-dose series of IPV at ages 2, 4, 6 through 18 months, and 4 through 6 years. The final dose in the series should be administered on or after the fourth birthday and at least 6 months after the previous dose.

Catch-up vaccination:

- In the first 6 months of life, minimum age and minimum intervals are only recommended if the person is at risk of imminent exposure to circulating poliovirus (i.e., travel to a polio-endemic region or during an outbreak).
- If 4 or more doses are administered before age 4 years, an additional dose should be administered at age 4 through 6 years and at least 6 months after the previous dose.
- A fourth dose is not necessary if the third dose was administered at age 4 years or older and at least 6 months after the previous dose.
- If both oral polio vaccine (OPV) and IPV were administered as part of a series, a total of 4 doses should be administered, regardless of the child's current age. If only OPV was administered, and all doses were given prior to age 4 years, 1 dose of IPV should be given at 4 years or older, at least 4 weeks after the last OPV dose.
- IPV is not routinely recommended for U.S. residents aged 18 years or older.
- For other catch-up guidance, see Figure 2.

C For further guidance on the use of the vaccines mentioned below, see: www.cdc.gov/vaccines/hcp/acip-recs/index.html.

7. **Influenza vaccines. (Minimum age: 6 months for inactivated influenza vaccine [IIV], 18 years for recombinant influenza vaccine [RIV])**
Routine vaccination:
- Administer influenza vaccine annually to all children beginning at age 6 months. For the 2016–17 season, use of live attenuated influenza vaccine (LAIV) is not recommended.

For children aged 6 months through 8 years:
- For the 2016–17 season, administer 2 doses (separated by at least 4 weeks) to children who are receiving influenza vaccine for the first time or who have not previously received ≥2 doses of trivalent or quadrivalent influenza vaccine before July 1, 2016. For additional guidance, follow dosing guidelines in the 2016–17 ACIP influenza vaccine recommendations (see *MMWR* August 26, 2016;65(5):1-54, available at www.cdc.gov/mmwr/volumes/65/rr/pdfs/rr6505.pdf).
- For the 2017–18 season, follow dosing guidelines in the 2017–18 ACIP influenza vaccine recommendations.

For persons aged 9 years and older:
- Administer 1 dose.

8. **Measles, mumps, and rubella (MMR) vaccine. (Minimum age: 12 months for routine vaccination)**
Routine vaccination:
- Administer a 2-dose series of MMR vaccine at ages 12 through 15 months and 4 through 6 years. The second dose may be administered before age 4 years, provided at least 4 weeks have elapsed since the first dose.
- Administer 1 dose of MMR vaccine to infants aged 6 through 11 months before departure from the United States for international travel. These children should be revaccinated with 2 doses of MMR vaccine, the first at age 12 through 15 months (12 months if the child remains in an area where disease risk is high), and the second dose at least 4 weeks later.
- Administer 2 doses of MMR vaccine to children aged 12 months and older before departure from the United States for international travel. The first dose should be administered on or after age 12 months and the second dose at least 4 weeks later.

Catch-up vaccination:
- Ensure that all school-aged children and adolescents have had 2 doses of MMR vaccine; the minimum interval between the 2 doses is 4 weeks.

9. **Varicella (VAR) vaccine. (Minimum age: 12 months)**
Routine vaccination:
- Administer a 2-dose series of VAR vaccine at ages 12 through 15 months and 4 through 6 years. The second dose may be administered before age 4 years, provided at least 3 months have elapsed since the first dose. If the second dose was administered at least 4 weeks after the first dose, it can be accepted as valid.

Catch-up vaccination:
- Ensure that all persons aged 7 through 18 years without evidence of immunity (see *MMWR* 2007;56[No. RR-4], available at www.cdc.gov/mmwr/pdf/rr/rr5604.pdf) have 2 doses of varicella vaccine. For children aged 7 through 12 years, the recommended minimum interval between doses is 3 months (if the second dose was administered at least 4 weeks after the first dose, it can be accepted as valid); for persons aged 13 years and older, the minimum interval between doses is 4 weeks.

10. **Hepatitis A (HepA) vaccine. (Minimum age: 12 months)**
Routine vaccination:
- Initiate the 2-dose HepA vaccine series at ages 12 through 23 months; separate the 2 doses by 6 to 18 months.
- Children who have received 1 dose of HepA vaccine before age 24 months should receive a second dose 6 to 18 months after the first dose.
- For any person aged 2 years and older who has not already received the HepA vaccine series, 2 doses of HepA vaccine separated by 6 to 18 months may be administered if immunity against hepatitis A virus infection is desired.

Catch-up vaccination:
- The minimum interval between the 2 doses is 6 months.

Special populations:
- Administer 2 doses of HepA vaccine at least 6 months apart to previously unvaccinated persons who live in areas where vaccination programs target older children, or who are at increased risk for infection. This includes persons traveling to or working in countries that have high or intermediate endemicity of infection; men having sex with men; users of injection and non-injection illicit drugs; persons who work with HAV-infected primates or with HAV in a research laboratory; persons with clotting-factor disorders; persons with chronic liver disease; and persons who anticipate close, personal contact (e.g., household or regular babysitting) with an international adoptee during the first 60 days after arrival in the United States from a country with high or intermediate endemicity. The first dose should be administered as soon as the adoption is planned, ideally, 2 or more weeks before the arrival of the adoptee.

11. **Meningococcal vaccines. (Minimum age: 6 weeks for Hib-MenCY [MenHibrix], 2 months for MenACWY-CRM [Menveo], 9 months for MenACWY-D [Menactra], 10 years for serogroup B meningococcal [MenB] vaccines: MenB-4C [Bexsero] and MenB-FHbp [Trumenba])**
Routine vaccination:
- Administer a single dose of Menactra or Menveo vaccine at age 11 through 12 years, with a booster dose at age 16 years.
- For children aged 2 months through 18 years with high-risk conditions, see "Meningococcal conjugate ACWY vaccination of persons with high-risk conditions and other persons at increased risk" and "Meningococcal B vaccination of persons with high-risk conditions and other persons at increased risk of disease" below.

Catch-up vaccination:
- Administer Menactra or Menveo vaccine at age 13 through 18 years if not previously vaccinated.
- If the first dose is administered at age 13 through 15 years, a booster dose should be administered at age 16 through 18 years, with a minimum interval of at least 8 weeks between doses.
- If the first dose is administered at age 16 years or older, a booster dose is not needed.
- For other catch-up guidance, see Figure 2.

Clinical discretion:
- Young adults aged 16 through 23 years (preferred age range is 16 through 18 years) who are not at increased risk for meningococcal disease may be vaccinated with a 2-dose series of either Bexsero (0, ≥1 month) or Trumenba (0, 6 months) vaccine to provide short-term protection against most strains of serogroup B meningococcal disease. The two MenB vaccines are not interchangeable; the same vaccine product must be used for all doses.
- If the second dose of Trumenba is given at an interval of <6 months, a third dose should be given at least 6 months after the first dose; the minimum interval between the second and third doses is 4 weeks.

Meningococcal conjugate ACWY vaccination of persons with high-risk conditions and other persons at increased risk:
Children with anatomic or functional asplenia (including sickle cell disease), children with HIV infection, or children with persistent complement component deficiency (includes persons with inherited or chronic deficiencies in C3, C5-9, properdin, factor D, factor H, or taking eculizumab [Soliris]):
- **Menveo**
  - *Children who initiate vaccination at 8 weeks.* Administer doses at ages 2, 4, 6, and 12 months.
  - *Unvaccinated children who initiate vaccination at 7 through 23 months.* Administer 2 primary doses, with the second dose at least 12 weeks after the first dose AND after the first birthday.
  - *Children 24 months and older who have not received a complete series.* Administer 2 primary doses at least 8 weeks apart.
- **MenHibrix**
  - *Children who initiate vaccination at 6 weeks.* Administer doses at ages 2, 4, 6, and 12 through 15 months.
  - If the first dose of MenHibrix is given at or after age 12 months, a total of 2 doses should be given at least 8 weeks apart to ensure protection against serogroups C and Y meningococcal disease.

Fig. 1.8 (continued)

d For further guidance on the use of the vaccines mentioned below, see: www.cdc.gov/vaccines/hcp/acip-recs/index.html.

- **Menactra**
  - **Children with anatomic or functional asplenia or HIV infection**
    - *Children 24 months and older who have not received a complete series.* Administer 2 primary doses at least 8 weeks apart. If Menactra is administered to a child with asplenia (including sickle cell disease) or HIV infection, do not administer Menactra until age 2 years and at least 4 weeks after the completion of all PCV13 doses.
  - **Children with persistent complement component deficiency**
    - *Children 9 through 23 months.* Administer 2 primary doses at least 12 weeks apart.
    - *Children 24 months and older who have not received a complete series.* Administer 2 primary doses at least 8 weeks apart.
  - **All high-risk children**
    - If Menactra is to be administered to a child at high risk for meningococcal disease, it is recommended that Menactra be given either before or at the same time as DTaP.

Meningococcal B vaccination of persons with high-risk conditions and other persons at increased risk of disease:
Children with anatomic or functional asplenia (including sickle cell disease) or children with persistent complement component deficiency (includes persons with inherited or chronic deficiencies in C3, C5-9, properdin, factor D, factor H, or taking eculizumab [Soliris]):

- **Bexsero or Trumenba**
  - *Persons 10 years or older who have not received a complete series.* Administer a 2-dose series of Bexsero, with doses at least 1 month apart, or a 3-dose series of Trumenba, with the second dose at least 1–2 months after the first and the third dose at least 6 months after the first. The two MenB vaccines are not interchangeable; the same vaccine product must be used for all doses.

For children who travel to or reside in countries in which meningococcal disease is hyperendemic or epidemic, including countries in the African meningitis belt or the Hajj:

- Administer an age-appropriate formulation and series of Menactra or Menveo for protection against serogroups A and W meningococcal disease. Prior receipt of MenHibrix is not sufficient for children traveling to the meningitis belt or the Hajj because it does not contain serogroups A or W.

For children at risk during an outbreak attributable to a vaccine serogroup:

- For serogroup A, C, W, or Y: Administer or complete an age- and formulation-appropriate series of MenHibrix, Menactra, or Menveo.
- For serogroup B: Administer a 2-dose series of Bexsero, with doses at least 1 month apart, or a 3-dose series of Trumenba, with the second dose at least 1-2 months after the first and the third dose at least 6 months after the first. The two MenB vaccines are not interchangeable; the same vaccine product must be used for all doses.

For MenACWY booster doses among persons with high-risk conditions, refer to *MMWR* 2013;62(RR02):1-22, at www.cdc.gov/mmwr/preview/mmwrhtml/rr6202a1.htm, *MMWR* June 20, 2014 / 63(24):527-530, at www.cdc.gov/mmwr/pdf/wk/mm6324.pdf, and *MMWR* November 4, 2016 / 65(43):1189-1194, at www.cdc.gov/mmwr/volumes/65/wr/pdfs/mm6543a3.pdf.
For other catch-up recommendations for these persons and complete information on use of meningococcal vaccines, including guidance related to vaccination of persons at increased risk of infection, see meningococcal *MMWR* publications, available at: www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/mening.html.

12. **Tetanus and diphtheria toxoids and acellular pertussis (Tdap) vaccine. (Minimum age: 10 years for both Boostrix and Adacel)**
Routine vaccination:
- Administer 1 dose of Tdap vaccine to all adolescents aged 11 through 12 years.
- Tdap may be administered regardless of the interval since the last tetanus and diphtheria toxoid-containing vaccine.
- Administer 1 dose of Tdap vaccine to pregnant adolescents during each pregnancy (preferably during the early part of gestational weeks 27 through 36), regardless of time since prior Td or Tdap vaccination.

Catch-up vaccination:
- Persons aged 7 years and older who are not fully immunized with DTaP vaccine should receive Tdap vaccine as 1 dose (preferably the first) in the catch-up series; if additional doses are needed, use Td vaccine. For children 7 through 10 years who receive a dose of Tdap as part of the catch-up series, an adolescent Tdap vaccine dose at age 11 through 12 years may be administered.
- Persons aged 11 through 18 years who have not received Tdap vaccine should receive a dose, followed by tetanus and diphtheria toxoids (Td) booster doses every 10 years thereafter.
- Inadvertent doses of DTaP vaccine:
  - If administered inadvertently to a child aged 7 through 10 years, the dose may count as part of the catch-up series. This dose may count as the adolescent Tdap dose, or the child may receive a Tdap booster dose at age 11 through 12 years.
  - If administered inadvertently to an adolescent aged 11 through 18 years, the dose should be counted as the adolescent Tdap booster.
- For other catch-up guidance, see Figure 2.

13. **Human papillomavirus (HPV) vaccines. (Minimum age: 9 years for 4vHPV [Gardasil] and 9vHPV [Gardasil 9])**
Routine and catch-up vaccination:
- Administer a 2-dose series of HPV vaccine on a schedule of 0, 6-12 months to all adolescents aged 11 or 12 years. The vaccination series can start at age 9 years.
- Administer HPV vaccine to all adolescents through age 18 years who were not previously adequately vaccinated. The number of recommended doses is based on age at administration of the first dose.
- For persons initiating vaccination before age 15, the recommended immunization schedule is 2 doses of HPV vaccine at 0, 6-12 months.
- For persons initiating vaccination at age 15 years or older, the recommended immunization schedule is 3 doses of HPV vaccine at 0, 1–2, 6 months.
- A vaccine dose administered at a shorter interval should be readministered at the recommended interval.
  - In a 2-dose schedule of HPV vaccine, the minimum interval is 5 months between the first and second dose. If the second dose is administered at a shorter interval, a third dose should be administered a minimum of 12 weeks after the second dose and a minimum of 5 months after the first dose.
  - In a 3-dose schedule of HPV vaccine, the minimum intervals are 4 weeks between the first and second dose, 12 weeks between the second and third dose, and 5 months between the first and third dose. If a vaccine dose is administered at a shorter interval, it should be readministered after another minimum interval has been met since the most recent dose.

Special populations:
- For children with history of sexual abuse or assault, administer HPV vaccine beginning at age 9 years.
- Immunocompromised persons*, including those with human immunodeficiency virus (HIV) infection, should receive a 3-dose series at 0, 1–2, and 6 months, regardless of age at vaccine initiation.
- Note: HPV vaccination is not recommended during pregnancy, although there is no evidence that the vaccine poses harm. If a woman is found to be pregnant after initiating the vaccination series, no intervention is needed; the remaining vaccine doses should be delayed until after the pregnancy. Pregnancy testing is not needed before HPV vaccination.

*See *MMWR* December 16, 2016;65(49):1405-1408, available at www.cdc.gov/mmwr/volumes/65/wr/pdfs/mm6549a5.pdf.

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Fig. 1.8 (continued)

was an undeniable influence on the Americas from its beginning as Europeans colonized the New World. Inoculation by variolation was instrumental in the eventual eradication of smallpox and served as the first form of vaccination. Vaccines, first attributed to Edward Jenner, with his trials and experiments using what we now call "evidence-based medicine" were developed by way of the scientific method. Vaccine development through the nineteenth and twentieth centuries has resulted in the eradication of smallpox, is close to eradicating polio, and is responsible for the elimination of many diseases locally and regionally. In the United States, there has been a 99% decrease in incidence of the nine diseases for which vaccines have been recommended for decades accompanied by a similar decline in mortality and disease sequelae [9]. These diseases include smallpox, diphtheria, tetanus, pertussis, paralytic poliomyelitis, measles, mumps, rubella (including congenital rubella syndrome), and *Haemophilus influenzae* type b. Today, there are 26 different diseases listed by the WHO for which there exist vaccines to prevent them. These vaccines are available worldwide with many more VPD vaccines (24 to date) in development, many with likely approval within the next few years to the next decade.

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