

Vaccines

Katherine V. Houser, Myra Happe, Rachel Bean, and Emily E. Coates

INTRODUCTION

Vaccines are clinically simple but immunologically complex interventions that can dramatically reduce morbidity and mortality due to diseases across all age groups. Vaccines offer an elegant solution to infectious diseases as they provide a societal benefit that reaches beyond individual protection. Vulnerable community members whose immune systems are less able to adequately respond to vaccines (newborns, immunocompromised persons, the elderly) or who are unable to receive vaccines (due to allergy or a medical contraindication) depend on immunization of surrounding community members for protection against vaccine-preventable diseases. In pregnant women, vaccinations may offer the double benefit of protecting both mother and infant against the targeted pathogen.¹

While older adults (>65 years old) experience high proportions of the total morbidity and mortality for several vaccine-preventable diseases (e.g., seasonal influenza, pneumococcal disease, herpes zoster) due to immunosenescence, they are less able to mount their own protective immune responses after vaccination. Vaccination of children, who are the primary spreaders of many vaccine-preventable infectious diseases, and younger adults can provide dramatic reductions in disease incidence in older adults through community protection. Despite suboptimal vaccine responses with aging, several vaccines are specifically recommended for older adults. In addition, some vaccines for older adults now employ novel strategies to enhance immunogenicity, including higher antigen doses² and the addition of an adjuvant.³

Vaccines against microbes are increasingly appreciated for their potential role in the heightening battle against antimicrobial-resistant pathogens. Preventing an illness through vaccination obviates the need to treat a bacterial infection with antibiotics, thereby avoiding potential induction of antibiotic resistance in either the targeted pathogenic bacterium or the patient's healthy microbiota. The sparing of antimicrobial use to prevent the emergence of resistance can be considered another form of public health intervention provided by vaccines.

Over the last 300 years, vaccinology has made impressive advances in combating human suffering and death caused by infectious diseases. These advances have accelerated rapidly in the past century with the explosion of knowledge in microbiology, immunology, and genetics. Current scientific understanding has answered many questions about immunity and how to provide it through vaccination, yet significant challenges remain and are joined by emerging epidemic and pandemic infectious diseases with alarming regularity. The next-generation tools of rational vaccine design are anticipated to yield important and life-saving innovations.

This chapter first reviews selected events in the history of vaccination. The remarkable accomplishments that have resulted from programs of vaccination to date are then highlighted. We review important recent milestones in vaccine development strategies that have the potential to revolutionize the field and offer great hope for unmet vaccine needs. Vaccine development in response to recent epidemics and pandemics is reviewed. Current vaccination recommendations in the United States and around the world are then summarized. Finally, we discuss present and future challenges for the field of vaccinology.



CLINICAL RELEVANCE

- Vaccines are highly effective interventions for preventing infectious diseases with public health importance.
- Both individual protection and community (herd) immunity result from vaccination programs.
- The reductions in disease burden (morbidity and mortality) achieved through implementation of childhood vaccination programs are extraordinary.
- Vaccination is not just for children: in recent years, new adolescent and adult vaccines have become available and are now recommended.
- Clinicians of all specialties should take vaccine histories and provide access to vaccines relevant to their patients' ages and medical conditions. Access can be provided through referral or by stocking and administering the indicated vaccines.

HISTORY OF VACCINATION

The earliest known vaccines were against smallpox and were used in Asia in the second millennium. The practice was called variolation and involved exposing, usually through the intranasal route, a susceptible person to material from the dried scabs of a smallpox victim. If the recipient survived, she/he was protected against future smallpox disease. Since natural smallpox had a 30% mortality rate, and variolation had a lower (~1%) mortality rate, this ancient practice was an early example of weighing the risk-to-benefit ratio for a human health intervention. By the 1700s, variolation was employed in societies in Africa, India, the Ottoman Empire, England, and France (https://www.nlm.nih.gov/exhibition/smallpox/sp_variolation.html). The practice of variolation involved inherent risks, including occasional outbreaks of a mild form of the disease.

An English physician was searching for a safer alternative to variolation and would become known as the father of vaccinology. Dr. Edward Jenner performed a smallpox vaccination experiment on James Phipps on May 14, 1796, using cowpox pus from lesions on the hands of a milkmaid.⁴ Dr. Jenner then collected lesion material from a smallpox patient to use as a viral challenge. Phipps survived both the vaccination and the challenge.

Dr. Jenner's work was disliked by some because of the introduction of a cow virus into humans. Other opponents of vaccination were those with financial interests in lucrative variolation practices. When vaccination in England was made compulsory by the Vaccination Act of 1853, an organized anti-vaccine movement quickly arose. Incredibly, even in the present day and despite the evidence supporting the safety and effectiveness of licensed vaccines, organized anti-vaccine movements continue to challenge contemporary clinicians and public health officials. The internet and social media have facilitated self-publication with rapid wide dissemination of misinformation, anti-vaccine propaganda, and pseudoscience that circumvent traditional scientific peer review to feed on the general public's fears and misunderstandings.

KEY CONCEPTS

Jenner's Work on Smallpox Vaccination Highlights Many Dimensions Relevant for Translational Vaccinology Today

- **Disease burden, surveillance, epidemiology** A significant and unacceptable burden of smallpox disease drove development of a safer intervention to improve public health.
- **Innovation** Jenner's innovation resulted from the need for an improved biomedical intervention to address the significant risk of harm associated with the centuries-old variolation practice.
- **Clinical insight** An observation that dairymaids who had recovered from an occupational illness (cowpox) were seldom affected by smallpox led to Jenner's promotion of smallpox vaccination. The observation of the protected state (immunity) in dairymaids led to a concept that was tested and promoted by Jenner.
- **Post-vaccination challenge** After the vaccination procedure, Jenner's subjects were subsequently intentionally exposed to (challenged with) wild-type smallpox and observed for safety and disease outcomes. Human challenge with smallpox would not be considered ethical today, although human challenge experiments are performed when developing vaccines for certain self-limited or treatable infectious diseases.
- **Presentation of experimental results** To disseminate his scientific findings and advocate for wider vaccination deployment, Jenner presented his work to the Royal Society and then self-published his manuscript after it was rejected for publication.
- **Branding** The name "vaccination" was applied to the intervention. Vacca is the Latin word for cow.
- **Anti-vaccination movement and conflicts of interest** Jenner experienced significant opposition to his vaccine from groups opposed to the new technique and from individuals with variolation practices who faced financial losses as public acceptance of vaccination grew.

While Dr. Jenner's smallpox challenge experiment presented a high risk to the participant that may be questioned by today's standards, certain human challenge studies remain safe, acceptable, and valuable today. Human challenge studies are performed for self-limited and/or treatable infections in order to study vaccine and therapeutic efficacy or to characterize the host response to the infection in detail, for example, influenza,⁵ primary dengue,⁶ norovirus,⁷ and malaria.⁸ A human challenge experiment can rapidly provide feedback to vaccine developers and public health officials to help prioritize resource-intensive field trial evaluations of promising candidate vaccines. If an encouraging preliminary efficacy signal is observed in a post-vaccination human challenge trial, it may support vaccine approval by regulatory agencies. In 2020 the US Food and Drug Administration (FDA) approved a single-dose live oral cholera vaccine, Vaxchora, targeting *Vibrio cholerae* serogroup O1, representing

the first time human challenge data have supported vaccine approval by the FDA. For the pivotal efficacy trial, participants received vaccination with Vaxchora, followed by controlled human infection with *Vibrio cholerae*.⁹ Vaccine efficacy was found to be 90% at 10 days and 80% at 3 months post-vaccination.

A second phase of vaccination's history ensued over the nineteenth century with the emergence of the germ theory, in which infectious diseases were caused by microorganisms too small to be seen without magnification. Robert Koch (1843–1910) and Louis Pasteur (1822–1895) contributed many key observations and experiments regarding both infectious diseases and vaccines. Koch's four postulates laid out the requirements for establishing causality of infectious diseases by microbes and proved that *Bacillus anthracis* was the cause of anthrax, providing the first proof of a microbial etiology of a specific disease. Through attenuation or inactivation of the wild-type microbes, Pasteur produced vaccines that induced protection against a number of diseases. He performed a number of classical vaccination and challenge experiments to show that vaccines would protect susceptible farm animals from devastating veterinary pathogens like chicken cholera and anthrax, or human pathogens like rabies.¹⁰

In the early twentieth century, passive immunization was developed as a therapy for infectious diseases. While active immunization involves administering a vaccine to trigger a protected state (immunity), passive immunization involves transferring the protective proteins (antibodies) from an immune donor to a susceptible patient without administering a vaccine. Emil von Behring administered sera from immune horses to humans to cure and prevent diphtheria and was awarded the Nobel Prize in 1901 for his work (http://www.nobelprize.org/nobel_prizes/medicine/laureates/1901/behring-facts.html).

Laboratory growth of poliovirus permitted the development of both the inactivated polio vaccine (IPV; Salk, licensed in 1955) and the live-attenuated oral polio vaccine (OPV; Sabin, monovalent licensed in 1961, trivalent in 1963). As a result of those vaccines, poliovirus type 2 was eradicated in 1999, and no wild-type poliovirus type 3 has been detected since 2012. A historic milestone occurred in August 2020, when after four years of no new reported cases, Africa was officially declared poliovirus type 1 free (<https://www.cdc.gov/polio/why-it-matters/africa-kicks-out-wild-polio.htm>). However, it remains endemic in other regions. According to CDC, there were 176 cases of poliovirus type 1 reported in two countries in 2019: 29 (16%) in Afghanistan and 147 (84%) in Pakistan. In February 2022, after five years of no cases reported in Africa, a case of wild-type poliovirus type I was detected in a young child in Lilongwe, Malawi. However, due to the isolate being genetically linked to a sequence in Pakistan's Sindh Province, the continent's wild poliovirus-free certification remains unaffected ([https://www.who.int/emergencies/disease-outbreak-news/item/wild-poliovirus-type-1-\(WPV1\)-malawi](https://www.who.int/emergencies/disease-outbreak-news/item/wild-poliovirus-type-1-(WPV1)-malawi)). While the progress toward global polio eradication is impressive, final eradication will require internationally coordinated efforts, persistence in vaccinating endemic countries' populations, and sustained attention to surveillance.

Several other live attenuated viral vaccines developed in the late twentieth century, such as measles, mumps, and rubella, have become staples of childhood vaccination programs in the US and globally. The development of the Oka strain of the varicella zoster virus led to live attenuated vaccines for both chicken pox in children and herpes zoster in older adults. To produce these vaccines, the serial passage of wild-type viruses promotes viral adaptation for growth in cell cultures and diminishes virulence in humans. Importantly, these attenuated vaccine-strain

viruses are not only well-tolerated and safe in humans but retain the ability to provoke protective immune responses.

Recognition and subsequent exploitation of key antigenic substructures rather than whole microbes were important technical advances. The studies of the polysaccharide capsules of *Streptococcus pneumoniae*¹¹ and M proteins of *Streptococcus* species,¹² respectively, led to characterization, isolation, and serotyping of these bacterial structures and their recognition as key antigens in immunity to Streptococcal diseases. Such observations led eventually to safer vaccination with components (subunits) of pathogens, as opposed to entire microbes. When delivered as vaccines, these isolated microbial components produce protective antibody and cellular immune responses but do not cause the disease induced by the complete wild-type organisms.

The polysaccharide vaccines developed for the prevention of bacterial diseases caused by *Haemophilus influenzae*, *Neisseria meningitidis*, and *Streptococcus pneumoniae* were also welcome advances. These bacterial polysaccharides were covalently coupled, or conjugated, to a protein carrier such as tetanus or diphtheria toxoids. This maneuver converted the T-cell-independent polysaccharide vaccines into T-cell-dependent protein-polysaccharide conjugate vaccines and resulted in B cell memory, improved immunity, utility in newborns, and herd immunity.¹³

The molecular biology revolution of the Twenty-First Century, in particular recombinant DNA technology, along with fundamental dissections of the innate and adaptive immune responses, have generated novel approaches to vaccination. Some of these next-generation vaccine platforms, including nucleic acid vaccines and viral-vectored vaccines, are discussed further in the sections below.

ACCOMPLISHMENTS OF VACCINATION

It is generally believed that elimination of an infectious disease from human circulation through vaccination can be achieved only when the following conditions are met: (1) the pathogen has no animal reservoir, and (2) the vaccine induces long-lasting immunity (Table 87.1). Smallpox eradication was achieved

TABLE 87.1 Stages of Reduction of Infectious Disease Incidence by Vaccination and Other Prevention Interventions

- **Control.** The reduction of disease incidence and prevalence to a locally acceptable level due to vaccination and/or other interventions; continued interventions are needed to maintain the reduction. Example: diarrheal diseases.
- **Elimination of disease.** Reduction to zero of the incidence of a specified disease in a defined geographical area as a result of vaccination and/or other interventions; continued measures are required. Example: neonatal tetanus.
- **Elimination of infection.** Reduction to zero of the incidence of infection caused by a specific agent in a defined geographical area as a result of vaccination and/or other interventions; continued measures to prevent re-establishment of transmission are required. Example: poliomyelitis elimination from North America.
- **Eradication.** Permanent reduction to zero of the worldwide incidence of infection due to a specific agent as a result of vaccination and/or other prevention efforts; interventions are no longer needed. Example: smallpox.
- **Extinction.** An infectious agent no longer exists in either nature or the laboratory. Example: none.

Adapted from Dowdle WR. The principles of disease elimination and eradication. *Bull World Health Organ*. 1998;76(suppl 2):22–25.

after a worldwide vaccination campaign and is the signature accomplishment of vaccination. The fields of medicine and public health celebrate this remarkable success as it showcases the power of vaccines to improve human health. Smallpox was a scourge of humanity for millennia, disfiguring and blinding survivors and killing 30% of those infected. The world's last known naturally occurring smallpox case occurred in Somalia in 1977. After the disease was eliminated, routine vaccination against smallpox in the general public was discontinued since it was no longer necessary for prevention. In 1980, the World Health Organization (WHO) certified that smallpox had been eradicated.¹⁴

The US Centers for Disease Control and Prevention (CDC) designated vaccination as first on the list of the ten greatest public health achievements of the twentieth century,¹⁵ and the WHO named “Vaccine Hesitancy” as one of the “Ten threats to global health in 2019” (<https://www.who.int/news-room/spotlight/ten-threats-to-global-health-in-2019>). In addition to smallpox eradication, the control of many common childhood infections and attendant reductions in morbidity and mortality are great achievements. Implementation of routine US childhood immunization programs led to major reductions from mid-twentieth century disease peaks to record low levels for several infectious diseases today (Table 87.2). For example, in the US, the incidence of polio, measles, rubella, and mumps declined by 100%, 99.9%, 99.9%, and 95.9%, respectively.¹⁶ It is estimated that for each annual birth cohort of approximately four million US children, vaccines in the US childhood immunization schedule prevent an estimated 20 million cases of disease and 42,000 deaths.¹⁷ Furthermore, while it is true that a considerable investment of resources is required to complete the annual programs of childhood vaccination, vaccines result in very significant cost savings, hence are highly cost-effective interventions. For each annual US birth cohort, vaccines result in nearly \$14 billion in annual net direct cost savings and \$69 billion in annual net societal cost savings, including reductions in parental missed work to care for an ill child.¹⁷

TABLE 87.2 Historical Comparisons of Morbidity and Mortality for Vaccine-Preventable Diseases in the United States

Disease	Pre-Vaccination: Estimated Annual Average Number of Cases	Post Vaccination: Annual Cases (Reported or Estimated) in Year 2006	% Reduction
Diphtheria	21,053	0	100
Measles	530,217	55	99.9
Mumps	162,344	6,584	95.9
Pertussis	200,752	15,632	92.2
Paralytic Poliomyelitis	16,316	0	100
Rubella	47,745	11	99.9
Smallpox	29,005	0	100
Tetanus	580	41	92.9
Hepatitis A	117,333	15,296	87
Acute hepatitis B	66,232	13,169	80.1
Invasive Hib	20,000	<50	99.8
Invasive pneumococcal disease	63,067	41,550	34.1
Varicella	4,085,120	48,445	85

Adapted from Roush SW, Murphy TV. Vaccine-Preventable Disease Table Working Group. Historical comparisons of morbidity and mortality for vaccine-preventable diseases in the United States. *JAMA*. 2007;298(18):2155–2163.

Vaccines protect the recipient against disease and reduce transmission of disease-causing microbes to unvaccinated persons. The term for this protection is herd immunity or community immunity. A disease that has been studied closely with regard to community immunity is measles. Measles is highly contagious and easily recognizable in epidemic form. Clustering of poor vaccination coverage often occurs in communities, as demonstrated in recent measles outbreaks in the United States. In 2019, CDC reported 1282 individual cases reported in 31 states, the largest number of cases reported in the US since 1992. The majority of these cases (~89%) were among people who were not vaccinated or whose vaccination status was unknown.¹⁸ Such outbreaks point out the importance of community immunity to protect vulnerable (unvaccinated) members of our communities. Given that many of the recent measles outbreaks in the United States have been linked to imported cases, another important lesson is that as long as a vaccine-preventable, highly transmissible infectious disease exists anywhere, it remains a potential threat everywhere—and global vaccination programs will continue to be important to ensure the health of all community members.

Another powerful example of vaccine-induced community immunity comes from pneumococcal vaccines. There are many unique challenges relating to pneumococcal vaccines: a large number of circulating serotypes, suboptimal immunogenicity of polysaccharide-only vaccines, and noninvasive carriage of the organism. In spite of these, introduction of the pneumococcal conjugate vaccines in infants in 2000 not only led to decreased invasive disease among vaccinated children, but also produced a significant decrease in adults, particularly among older adults in whom this bacterium frequently causes pneumonia.¹⁹ The impact of this vaccine highlights the effectiveness of community immunity produced by vaccines.

Other recently introduced vaccines have made significant impact in relatively brief periods. Before the 2006 implementation of routine rotavirus vaccination, rotavirus infections were a significant cause of severe gastroenteritis in young children and accounted for an estimated 410,000 physician visits, 205,000 to 272,000 emergency department visits, and 55,000 to 70,000 hospitalizations annually with total costs of up to \$1 billion in the US alone. The licensure and approval of a rotavirus vaccine reduced hospitalizations by 70% to 80%.²⁰ Another example is the human papilloma virus (HPV) vaccine, a recombinant virus-like particle (VLP) vaccine for primary prevention of cancer. The US CDC Advisory Committee on Immunization Practices (ACIP) recommended routine HPV vaccination for young females in 2006 and for young males in 2011. Since the introduction of the HPV vaccine, there has been a significant reduction in HPV infections and cervical precancers. A comprehensive meta-analysis of more than 60 million HPV vaccinated individuals in 14 countries demonstrated that the rate of HPV 16 to 18 infections decreased by 83% among females 13 to 19 years of age and by 66% among those 20 to 24 years of age, whereas the prevalence of precancerous lesions decreased by 51% and 31%, respectively.²¹

Recent Changes in Vaccine Development Strategies

Early vaccines were live attenuated or inactivated versions of whole wild-type human pathogens, for example, rabies, yellow fever virus, and influenza. In a few cases, attenuated zoonotic organisms closely related to human pathogens were employed to produce cross-reactive protective responses in humans, for

example, vaccinia, an animal poxvirus utilized as a vaccine against human smallpox, and bacille Calmette-Guerin (BCG), an agent of bovine tuberculosis developed as a human tuberculosis vaccine. Later, split virus vaccines utilized partially purified protein antigens derived from whole inactivated viruses, for example, split virus influenza vaccines. The polysaccharide capsules of bacteria were purified from cultures of multiple serotypes of a single bacterial species leading to polyvalent polysaccharide vaccines; for example, the 23-valent pneumococcal polysaccharide and the quadrivalent meningococcal polysaccharide vaccines. Bacterial toxins were purified from cultures and made harmless by heat or chemical treatment to produce toxoid vaccines, for example, tetanus and diphtheria vaccines.

Recent decades have featured explosive discoveries in genetics, molecular biology, immunology, and microbiology, leading to new theory-based (so-called rational) approaches to vaccine design. These advances have led to structure-based vaccine design, generations of recombinant vaccines (based on combining two or more sources of DNA), recombinant viral-vectored vaccines, and nucleic acid-based vaccines (Table 87.3).

Advances in the development of a vaccine for respiratory syncytial virus (RSV) exemplify the impact of structural biology and molecular engineering on vaccine design. RSV is the leading cause of viral acute lower respiratory tract infections globally, with the highest burden of disease occurring in infants under six months of age.²² Despite nearly 60 years of research and development efforts, no licensed vaccine for RSV exists. In the 1960s, one clinical trial administering a formalin-inactivated RSV vaccine candidate (FI-RSV) in infants and young children resulted in the hospitalization of 80 percent of vaccine recipients, with two fatalities due to disease enhancement following natural RSV infection.²³ Twenty years after the trial, it was determined that while FI-RSV elicited antibodies in nearly all recipients, the majority were directed against nonprotective epitopes.²⁴ Structural biology became a prominent tool in demonstrating why FI-RSV preferentially produced non-neutralizing antibodies. The fusion (F) glycoprotein of RSV, required for viral entry into host cells, exists in two conformational states: pre-fusion (pre-F) and post-fusion (post-F). While the pre-F conformation is used for viral entry, it is metastable and irreversibly rearranges to a nonfunctional post-F state.²⁵ Due to the unstable structure of F, formalin

TABLE 87.3 Vaccine Platforms: Classical and Next-Generation

Platform Type	Subtype	Examples
Whole pathogen	Live attenuated	Measles, mumps, rubella, varicella zoster, yellow fever vaccines
	Inactivated	Rabies vaccine
Subunit	Polysaccharide	23-valent <i>Streptococcus pneumoniae</i> vaccine
	Polysaccharide conjugated to protein	13-valent <i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> , <i>Neisseria meningitidis</i> vaccines
	Protein	Influenza vaccine
	Virus-like particle	Human papillomavirus vaccine
Next-Generation	Viral vectored	Dengue, Ebola vaccines
	Nucleic acid based	Zika (in development) and SARS-CoV-2 vaccines
	Nanoparticle based	Influenza (in development)

inactivation in FI-RSV resulted in an almost entirely post-F antigen. Recent advances in structural biology and molecular engineering were prominent features in the design of a productive RSV antigen through the introduction of stabilizing mutations to preserve the pre-F conformation. The resulting antigen, DS-Cav1, is a stabilized trimer of the pre-F RSV F glycoprotein. This protein subunit vaccine elicited neutralizing titers 70 to 80 times greater than post-F antigens in mice and nonhuman primates. Advancing to phase 1 trials, DS-Cav1 was safe and tolerable in healthy adults and elicited neutralizing antibody responses with and without adjuvant.²⁵ The identification and stabilization of the pre-F conformation have led to the development of several types of vaccine candidates designed specifically for infants, the elderly, and pregnant women in the third trimester intended to provide passive immunity to the infant through the first months of life.²⁶ At the time of this writing, further clinical development and vaccine efficacy trial outcomes are highly anticipated.

Concurrent with the advances in structural biology that enabled progress in RSV vaccine development, advances in genetics and molecular biology allowed for gene cloning and expression in recombinant molecular systems, revolutionizing vaccine development. Vaccines can now be designed based on the *in vitro* expression of one or a few genes. For example, the hepatitis B vaccine, originally developed by Hilleman, was purified hepatitis B surface antigen (HBsAg) from the blood of chronically infected humans. But soon thereafter, a second licensed hepatitis B vaccine was produced in yeast cells through recombinant DNA methods that inserted the HBsAg gene into yeast organisms for expression and purification. In 1986, this hepatitis B vaccine was the first approved recombinant vaccine in the US (RECOMBIVAX HB) (<https://www.fda.gov/media/74274/download>). Newer generation vaccines have since been developed (ENGERIX-B [<https://www.fda.gov/media/119403/download>] and HEPLISAV-B [<https://www.fda.gov/media/108745/download>]) and are widely used today. This platform offers advantages including protein purity, as the genes of interest are expressed in relative isolation, and vaccine safety, as it is no longer necessary to derive vaccines by partially purifying the HBsAg from paid-donor plasma of humans chronically infected with hepatitis B virus (and potentially other viruses).

Novel recombinant vaccines and recombinant viral-vectored vaccines have been approved or recommended for human use for a number of pathogens, including HPV, malaria, and dengue, as discussed below.

Human Papillomavirus

The HPV vaccine is a highly effective recombinant VLP vaccine; its public health impacts were highlighted earlier in this chapter. Recombinant HPV L proteins expressed in recombinant systems form VLPs that are purified and formulated with or without an adjuvant. The most recent polyvalent vaccine expresses VLPs representing nine HPV serotypes (GARDASIL 9).²⁷ HPV VLP vaccines are remarkable for their efficacy and safety and because they are primary prevention for several types of cancer in both boys and girls.²⁸

Malaria

Malaria causes an annual global disease burden of 220 million cases and 400,000 deaths, with the vast majority of cases concentrated in Africa. Pregnant women and children under 5 are the

two highest-risk populations, and the development of an effective malaria vaccine remains a global health priority (<https://www.who.int/publications/i/item/world-malaria-report-2019>). The most advanced malaria vaccine, RTS,S, is a recombinant protein subunit vaccine that targets the pre-erythrocytic stage of the *Plasmodium falciparum* parasite. It was evaluated in combination with the adjuvant AS01 in a Phase 3 trial in which RTS,S/AS01 (Mosquirix) demonstrated 36.3% vaccine efficacy four years after first vaccination in children aged 5 to 17 months who received the four recommended doses.²⁹ Following the phase 3 results, two WHO advisory groups jointly called for pilot implementation of the vaccine in 3 to 5 African nations. In April 2017, the WHO approved the joint recommendation and established the Malaria Vaccine Implementation Programme (MVIP) to further evaluate the vaccine's safety profile and assess the feasibility of a four-dose vaccine administration before broader use across sub-Saharan Africa (https://www.who.int/immunization/sage/meetings/2018/april/2_WHO_MalariaMVIP-update_SAGE_Apr2018.pdf?ua=1). Three pilot countries, Malawi, Ghana, and Kenya, were selected based on pre-specified criteria. In May 2018, the vaccine was approved by each country's national regulatory agency, and the first round of administration began in April 2019. In October 2021, after more than 2.3 million doses of the vaccine had been administered to over 800,000 children in the pilot nations, the WHO recommended RTS,S/AS01 for broad use in children in sub-Saharan Africa and other regions with moderate to high *Plasmodium falciparum* malaria transmission. The MVIP is anticipated to conclude in 2023 once the potential benefits of a 4th dose and longer-term effects on childhood deaths have been assessed (<https://www.who.int/news/item/06-10-2021-who-recommends-groundbreaking-malaria-vaccine-for-children-at-risk>).

Dengue

There are an estimated 390 million infections of the dengue virus globally each year, with 95 million of those infections resulting in clinical disease.³⁰ In 2019, the first dengue vaccine was approved in several countries, including by the US FDA, for use in dengue-endemic regions. This vaccine, Dengvaxia (CYD-TDV), is a recombinant live tetravalent viral vector based on the yellow fever virus vaccine strain 17D expressing the envelope and pre-membrane genes of all four dengue serotypes. Dengvaxia has been administered to more than 41,000 individuals across 26 clinical trials, with a favorable safety and immunogenicity profile.³¹ Based on promising results, vaccination campaigns were launched in both Brazil and the Philippines, which included school-aged children. However, long-term observation of vaccine recipients revealed an increased risk of severe dengue disease in individuals who had no previous exposure to dengue at the time of vaccination (*i.e.*, baseline seronegative individuals) and in young children (regardless of serostatus).³¹ During the vaccination campaigns in Brazil and the Philippines, 87 cases of dengue infection were reported, with 14 resulting in fatalities. Following an additional investigation by the WHO Global Advisory Committee on Vaccine Safety, no causality determination could be made for these fatalities.³² Based on this increased risk of severe dengue infection in seronegative vaccine recipients, Dengvaxia is indicated only for seropositive individuals aged 9 to 45 years.³³ The results from the long-term follow-up of Dengvaxia had a detrimental impact on vaccine confidence, particularly in the Philippines. In that country, increased vaccine hesitancy is believed to have contributed to a widespread measles outbreak in 2019.³⁴

Recombinant viral vectored vaccines, such as Dengvaxia, the Ebola vaccine Ervebo, which will be discussed later in this chapter, and

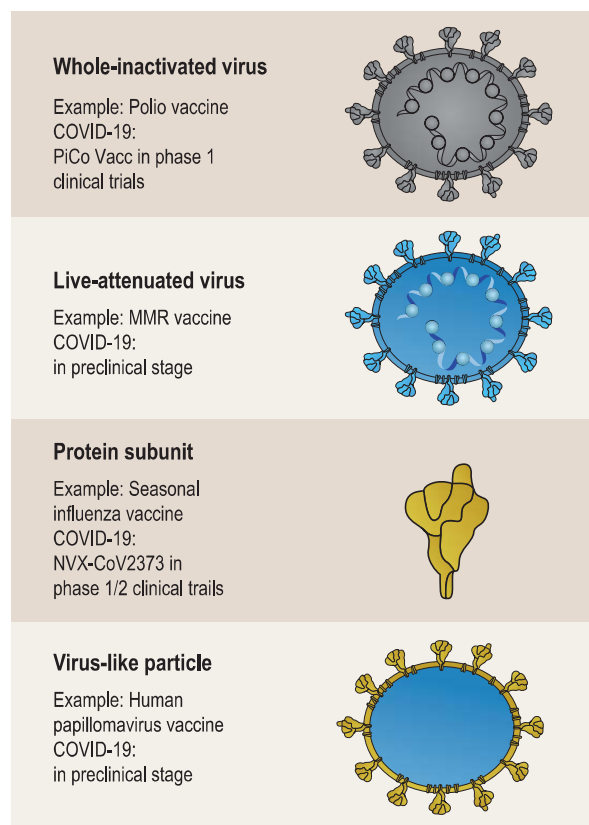
nucleic acid vaccines represent the next generation of vaccine technology. DNA vaccines utilize DNA plasmids as a vector for expressing pathogen antigens *in vivo*, while mRNA is packaged in a carrier molecule for cellular delivery, most often a lipid nanoparticle. The technology has been utilized for rapid vaccine production in response to outbreaks such as Zika and the COVID-19 global pandemic, which began in 2019.^{35–37} In August 2021, COMIRNATY®, a COVID-19 mRNA vaccine developed by BioNTech and Pfizer, became the first nucleic acid-based vaccine to receive approval from the US FDA for use in humans (<https://www.fda.gov/news-events/press-announcements/fda-approves-first-covid-19-vaccine>). A second vaccine for COVID-19 using mRNA technology, SPIKEVAX® manufactured by Moderna, received FDA approval shortly after in January 2022 (<https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/spikevax-and-moderna-covid-19-vaccine>). Fig. 87.1 portrays a schematic of both classical and next-generation platforms in the context of COVID-19 vaccine development, and additional discussion of the pandemic and the response is included later in this chapter.

Adjuvants

The magnitude of immune responses can be improved by adding compounds called *adjuvants* to vaccine formulations. Recent ad-

vances in our understanding of the innate immune system have led to an appreciation that adjuvants act primarily through their effects on innate immunity. Adjuvant-triggered innate signals enhance the quantity, quality, and specificity of the downstream adaptive immune responses to the vaccine antigen. Adjuvants are also used to promote increased rates of seroconversion and induce immunity even in populations with less responsive immune systems such as the elderly, infants, and immunocompromised. Another advantage of adjuvants relates to dose-sparing, or their ability to reduce the amount of antigen used or the number of vaccine administrations given to produce comparable immune responses.³⁸ Some of the most widely used, clinically approved adjuvants are aluminum-based, such as aluminum hydroxide (AH) and aluminum phosphate (AP). These adjuvants primarily function to amplify antibody production in response to vaccine antigens. Although aluminum adjuvants have been used for many decades, the exact mechanism underlying their immune enhancement properties is not fully understood. Aluminum adjuvants generally have safe profiles and are included in vaccine formulations at very low doses (0.85 to 1.25 mg).^{39,40} Novel adjuvants in various stages of development include oil-in-water emulsions (e.g., MF059 and AS03), saponin-based adjuvants (e.g., QS-21), adjuvants targeting pattern recognition (e.g., CpG-ODN), and Toll-like receptor and RIG-I-like receptor ligand-specific adjuvants (e.g., TLR4).³⁸

Classical platforms



Next-generation platforms

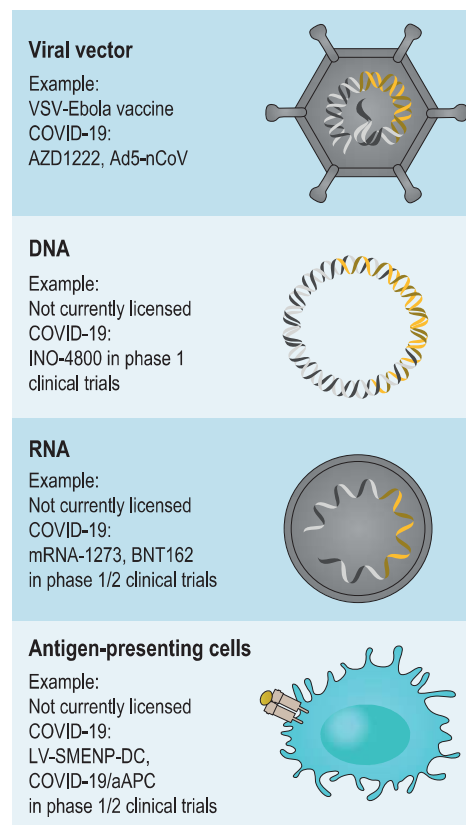


FIG. 87.1 An Overview of the Different Vaccine Platforms in Development Against COVID-19. A schematic representation is shown of the classical vaccine platforms that are commonly used for human vaccines, and next-generation platforms, where very few have been licensed for use in humans. The stage of development for each of these vaccine platforms for COVID-19 vaccine development is shown; online vaccine trackers are available to follow these vaccines through the clinical development and licensing process. (Reproduced from van Riel D, de Wit E. Next-generation vaccine platforms for COVID-19. *Nat Mater*. 2020;19[8]:810–812.) As of March 2022, two RNA vaccines are currently approved by the FDA for use in humans: COMIRNATY® (NCT04368728) and SPIKEVAX® (NCT04470427).

Systems Biology Approach to Vaccination

Over the last decade, systems biology, or systems vaccinology, approaches to vaccine development have captured considerable interest.⁴¹ The principal objectives of a systems vaccinology approach are to elucidate complex immunological pathways that generate long-lasting immunological memory and to provide new insights into molecular and cellular signatures that can predict vaccine efficacy. In addition to the traditional cellular and humoral immunological assays (antibodies, T cells, B cells), multiple “omics” assays may be performed and used to generate computer models or algorithms describing the immune response to vaccination. Some of the applications of “omics” assays include profiling of T-cell epitopes and antibody specificity by proteomics, the discovery of predictive biomarkers by metabolomics and lipidomics, assessment of host-pathogen interactions and infection-induced immune responses by transcriptomics, and mapping of antibody glycosylation by glycomics.⁴² Recent technological advances bring novel methods to systems vaccinology that include single-cell genomics and epigenomics. Single-cell technologies enable deconvolution and more in-depth resolution of immune responses by identifying cellular heterogeneity, rare cell subtypes, and unique biomarkers.⁴³ The use of new high-throughput assays to assess multiple dimensions of innate and adaptive immune responses generates very large data sets. Analyses and integration of these huge data sets require multidisciplinary collaboration with computational biologists and informaticians. These detailed assessments are being applied in a variety of infectious and non-infectious disease states. The impact of systems vaccinology on public health is yet to be fully realized; as the technologies supporting this approach continue to improve, new progress on vaccine development and utilization is anticipated.

Recent Responses to Epidemics and Pandemics

Despite all the advances and accomplishments of vaccine science, there remains a pressing public health concern that resonates around the globe, that is: when major epidemics of lethal and highly infectious diseases occur, can protective vaccines be developed quickly enough to respond? Advances in next-generation vaccine technology have allowed for record-speed product development over the last several years, most recently with the development of multiple COVID-19 vaccine candidates in a matter of months. Demonstrating vaccine efficacy during an ongoing epidemic or pandemic remains a challenge, and each outbreak presents unique hurdles. Below are three recent case studies of diseases that caused epidemics or pandemics and examples of vaccine development that occurred in response to these global events.

Ebola

Ebola was first discovered in 1976, and vaccine development began in the late 1990s with an initial phase 1 clinical trial of the first candidate vaccine in 2003.⁴⁴ Multiple iterations of the Ebola vaccine were developed and tested in Phase 1 clinical trials leading to refinement of the antigen design and platform approach, and testing of advanced candidates starting in 2014.^{45,46} One of these candidates, rVSV-ZEBOV (Ervebo), was approved by the US FDA in 2019 for the prevention of Ebola virus disease (EVD) after demonstration of efficacy in a ring-vaccination clinical trial in 2015–16 during the West Africa Ebola outbreak (<https://www.fda.gov/vaccines-blood-biologics/ervebo>).⁴⁷ The VSV-EBOV vaccine is unique in that it represents the first vaccine against

a filovirus to be approved in the United States and is from a novel class of vaccine based on a viral vector. VSV-EBOV is a live, attenuated recombinant vesicular stomatitis virus (VSV) in which the gene for the native envelope glycoprotein is replaced with the gene from the Ebola virus glycoprotein.⁴⁶ Additional candidate vaccines designed to prevent EVD and other filoviruses are under evaluation in clinical testing (NCT04041570, NCT03475056),⁴⁸ and a prime-boost vaccine regimen, Zabdeno® (Ad26.ZEBOV) and Mvabea® (MVA-BN-Filo), was granted Marketing Authorization from the European Medicines Agency for prophylactic use in individuals ages 1 and older in May 2020 (<https://www.who.int/news-room/questions-and-answers/item/ebola-vaccines>).

Zika Virus

Zika virus is a mosquito-borne flavivirus closely related to dengue that was first discovered in 1947 in Zika Forest, Uganda. This single-stranded positive sense RNA virus resulted in small human disease outbreaks over the years, but from 2015 to 2016 emerged and spread across the Americas, Africa, and other parts of the world (<https://www.who.int/news-room/fact-sheets/detail/zika-virus>). To date, a total of 86 countries and territories have reported evidence of mosquito-transmitted Zika infection.⁴⁹ In pregnant women, infections resulted in fetal microcephaly or other birth anomalies.⁵⁰ In general, healthy adults with symptomatic infections experience a mild to moderate self-limited viral illness which has been described as “mild dengue” and is mostly characterized by fever, rash, conjunctivitis, and arthritis. An increased association of Guillain-Barré syndrome with Zika infections has also been reported in multiple countries. Interestingly, it is believed that 80% of Zika infections are asymptomatic. In symptomatic infected adults, viremia persists for less than a week in most cases, but longer durations of viral RNA detection are reported in semen and urine.^{51,52}

The development of a vaccine emerged as a top priority of the US government’s response to the epidemic in 2015. Several leading candidates, including both inactivated and DNA vaccine platforms, were rapidly developed and evaluated in early phase clinical trials.^{36,53} One of the candidates progressed into a multinational efficacy trial in early 2017, but the epidemic waned before an efficacy signal could be detected.⁵⁴ However, these vaccine candidates, along with others that have shown promise in preclinical studies, remain in development in preparation for another Zika epidemic.

SARS-CoV-2

In January 2020, a novel coronavirus was identified as the cause of an outbreak in China. By late September 2020, SARS-CoV-2 quickly spread worldwide with over 1 million documented deaths due to the clinical disease, COVID-19.⁵⁵ Using techniques and expertise garnered from prior pandemic responses and pre-existing coronavirus (SARS-CoV-1 and MERS) vaccine research, publicly and privately funded vaccine research teams promptly developed candidate SARS-CoV-2 vaccines for the prevention of COVID-19 disease.^{56,57} The first documented COVID-19 vaccine clinical trial launched in the United States in March 2020 with multiple candidates entering clinical trials shortly after, quickly demonstrating safety and immunogenicity^{37,58–60} resulting in the launch of multiple phase 3 efficacy trials by mid to late 2020 (NCT04505722, NCT04516746, NCT04470427, NCT04368728).⁶¹ A variety of established and novel vaccine

platforms were developed predominantly expressing the SARS-CoV-2 spike protein with many specifically encoding for a stabilized version of the spike protein described in early 2020.⁵⁶ To enable rapid deployment of safe and efficacious vaccines, multiple international governments established vaccine research and production programs and the US government launched Operation Warp Speed (OWS) in May 2020, designed to utilize expertise and resources from the US government and private sectors working rapidly to develop and produce a vaccine for the US public, specifically to produce over 300 million safe and effective vaccine regimens for the US public by January of 2021. This effort funded and enabled the development of multiple candidate vaccines of various platform types (including nucleic acid, viral vector, and protein subunit).⁶¹ At the time of this writing, two nucleic acid vaccines have received FDA approval, COMIRNATY® and SPIKEVAX®, after demonstrating 93 to 95% efficacy against symptomatic disease in final analyses of the phase 3 trials (<https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-vaccines>).

Current Recommendations

Today in the United States, there are clear national guidelines that recommend vaccines for children, adolescents, and adults. Each February, the CDC publishes two recommended immunization schedules based on the recommendations of the CDC-appointed ACIP. One ACIP schedule of immunizations provides the adult immunization recommendations (Table 87.4). The adult schedule offers recommendations for each vaccine based on the age of the patient. For example, the ACIP recommends that all adults (persons aged 19 years and over) receive: annual influenza vaccination; tetanus-diphtheria-acellular pertussis (Tdap) vaccine once, followed by tetanus boosters every 10 years; a 2-dose recombinant zoster vaccine (RZV) administered 2 to 6 months apart for individuals aged ≥50 years; and a pneumococcal vaccination at age 65 years (<https://www.cdc.gov/vaccines/schedules/hcp/index.html>).

The adult schedule also provides recommendations for vaccines indicated for certain risk factors, including medical conditions (e.g., immunocompromising conditions, kidney failure, diabetes), pregnancy, and certain occupations. Importantly, live

TABLE 87.4 Parts A and B: Recommended Adult Immunization Table, United States, 2020, From the Advisory Committee on Immunization Practice of the Centers for Disease Control and Prevention

A				
Vaccine	19–26 years	27–49 years	50–64 years	≥65 years
Influenza inactivated (IIV4) or Influenza recombinant (RIV4)	1 dose annually			
Influenza live, attenuated (LAIV4)	1 dose annually			
Tetanus, diphtheria, pertussis (Tdap or Td)	1 dose Tdap each pregnancy; 1 dose Td/Tdap for wound management (see notes)			
	1 dose Tdap, then Td or Tdap booster every 10 years			
Measles, mumps, rubella (MMR)	1 or 2 doses depending on indication (if born in 1957 or later)			
Varicella (VAR)	2 doses (if born in 1980 or later)	2 doses		
Zoster recombinant (RZV)	2 doses for immunocompromising conditions (see notes)		2 doses	
Human papillomavirus (HPV)	2 or 3 doses depending on age at initial vaccination or condition	27 through 45 years		
Pneumococcal (PCV15, PCV20, PPSV23))	1 dose PCV15 followed by PPSV23 or 1 dose PCV20 (see notes)			1 dose PCV15 followed by PPSV23 or 1 dose PCV20
Hepatitis A (HepA)	2 or 3 doses depending on vaccine			
Hepatitis B (HepB)	2, 3, or 4 doses depending on vaccine or condition			
Meningococcal A, C, W,Y (MenACWY)	1 or 2 doses depending on indication, see notes for booster recommendations			
Meningococcal B (MenB)	2 or 3 doses depending on vaccine and indication, see notes for booster recommendations			
	19 through 23 years			
Haemophilus influenzae type b (Hib)	1 or 3 doses depending on indication			
<div><div></div> Recommended vaccination for adults who meet age requirement, lack documentation of vaccination, or lack evidence of past infection</div> <div><div></div> Recommended vaccination for adults with an additional risk factor or another indication</div> <div><div></div> Recommended vaccination based on shared clinical decision-making</div> <div><div></div> No recommendation/ Not applicable</div>				

TABLE 87.4 Parts A and B: Recommended Adult Immunization Table, United States, 2020, From the Advisory Committee on Immunization Practice of the Centers for Disease Control and Prevention—cont'd

B											
Vaccine	Pregnancy	Immuno-compromised (excluding HIV infection)	HIV infection CD4 percentage and count		Asplenia, complement deficiencies	End-stage renal disease, or on hemodialysis	Heart or lung disease; alcoholism ¹	Chronic liver disease	Diabetes	Health care personnel ²	Men who have sex with men
			<15% or <200 mm ³	≥15 and ≥200 mm ³							
IIV4 or RIV4	1 dose annually										
or LAIV4	Contraindicated					Precaution			1 dose annually		
Tdap or Td	1 dose Tdap each pregnancy	1 dose Tdap, then Td or Tdap booster every 10 years									
MMR	Contraindicated*	Contraindicated	1 or 2 doses depending on indication								
VAR	Contraindicated*	Contraindicated		2 doses							
RZV		2 doses at age ≥19 years			2 doses at age ≥50 year						
HPV	Not Recommended*	3 doses through age 26 years			2 or 3 doses through age 26 years depending on age at initial vaccination or condition						
Pneumococcal (PCV15, PCV20, PPSV23)		1 doses PCV15 followed by PPSV23 OR 1 dose PCV20(see notes)									
HepA						2 or 3 doses depending on vaccine					
HepB	3 doses (see notes)	2, 3, or 4 doses depending on vaccine or condition									
MenACWY		1 or 2 doses	depending on indication, see notes for			booster recommendations					
MenB	Precaution	2 or 3 doses depending on vaccine			and indication, see notes for booster recommendations						
Hib		doses HSCT ³ recipients only				1 dose					
<div><div>Recommended vaccination for adults who meet age requirement, lack documentation of vaccination, or lack evidence of past infection</div><div>Recommended vaccination for adults with an additional risk factor or another indication</div><div>Recommended vaccination based on shared clinical decision-making</div><div>Precaution—vaccination might be indicated if benefit of protection outweighs risk of adverse reaction</div><div>Contraindicated or not recommended—vaccine should not be administered. *Vaccinate after pregnancy.</div><div>No recommendation/Not applicable</div></div> <div>1. Precaution for LAIV does not apply to alcoholism. 2. See notes for influenza; hepatitis B; measles, mumps, and rubella; and varicella vaccinations. 3. Hematopoietic stem cell transplant.</div>											

Notes: Tetanus, diphtheria, and pertussis vaccination: Pregnancy: 1 dose Tdap during each pregnancy, preferable in early part of gestational weeks 27-36; wound management: Persons with 3 or more doses of tetanus-toxoid-containing vaccine: For clean and minor wounds, administer Tdap or Td if more than 10 years since last dose of tetanus-toxoid-containing vaccine; for all other wounds, administer Tdap or Td if more than 5 years since last dose of tetanus-toxoid-containing vaccine. Tdap is preferred for persons who have not previously received Tdap or whose Tdap history is unknown. If a tetanus-toxoid-containing vaccine is indicated for a pregnant woman, use Tdap. Zoster vaccination: Immunocompromising conditions (including HIV): RZV recommended for use for persons 19 years or older who are or will be immunodeficient of immunosuppressed because of disease or therapy. Pneumococcal vaccination: Age 19–64 years with certain underlying medical conditions or other risk factors who have not previously received a pneumococcal conjugate vaccine or whose previous vaccination history is unknown: 1 dose PCV15 or 1 dose of PCV20. If PCV15 is used, this should be followed by a dose of PPSV23 given at least 1 year after PCV15 dose. A minimum interval of 8 weeks between PCV15 and PPSV23 can be considered for adults with an immunocompromised condition, cochlear implant, or cerebrospinal fluid leak to minimize the risk of invasive pneumococcal disease caused by serotypes unique to PPSV23 in these vulnerable groups. Hepatitis B vaccination: HepB is not recommended in pregnancy due to lack of safety data in pregnant women. Meningococcal vaccination: Booster dose is recommended for those at increased risk due to an outbreak and if 5 or more years have passed since receiving MenACWY and 1 year or more since receiving MenB. Detailed information could be found at <https://www.cdc.gov/vaccines/schedules/downloads/adult/adult-combined-schedule.pdf>.

vaccines (varicella and MMR) are contraindicated for pregnant women, immunocompromised hosts, and HIV-infected individuals when the CD4+ T-cell absolute count is below 200 cells/mcl.

A second ACIP immunization schedule of immunizations covers birth to 18 years of age and catch-up recommendations for children or adolescents who have not received recommended vaccines (Table 87.5). The ministries of health for many European countries publish their own country-specific immunization schedules, and vaccination guidelines published by the WHO are utilized by many developing countries. The schedules are generally similar but with some region-specific differences. For example, the 2020 US ACIP immunization schedule for children recommends vaccinations against

ten viral diseases: hepatitis B, rotavirus, poliovirus, influenza, measles, mumps, rubella, varicella, hepatitis A, and human papilloma virus (HPV) (<https://www.cdc.gov/vaccines/schedules/hcp/index.html>). Preventive viral vaccines in the WHO-recommended routine immunization schedule for children include the same 10 viral vaccines (although four—mumps, influenza, varicella, and hepatitis A vaccines—are recommended only for country immunization programs with certain characteristics). The WHO schedule also recommends additional vaccines, for example, rabies, yellow fever, Japanese encephalitis, and tick-borne encephalitis vaccines for certain high-risk populations (https://www.who.int/immunization/policy/immunization_tables/en/).

TABLE 87.5 Recommended Immunization Schedules for Persons Aged 0 Through 18 Years, United States, 2020, From the Advisory Committee on Immunization Practice of the Centers for Disease Control and Prevention

C																	
Vaccine	Birth	1 mo	2 mos	4 mos	6 mos	9 mos	12 mos	15 mos	18 mos	19–23 mos	2–3 yrs	4–6 yrs	7–10 yrs	11–12 yrs	13–15 yrs	16 yrs	17–18 yrs
Hepatitis B (HepB)	1 st dose	← -- 2 nd dose -- →			← ----- 3 rd dose ----- →												
Rotavirus (RV): RV1 (2-dose series), RV5 (3-dose series)			1 st dose	2 nd dose	See Notes												
Diphtheria, tetanus, acellular pertussis (DTaP <7 yrs)			1 st dose	2 nd dose	3 rd dose			← -- 4 th dose -- →				5 th dose					
Haemophilus influenzae type b (Hib)			1 st dose	2 nd dose	See Notes		3 rd or 4 th dose See Notes										
Pneumococcal conjugate (PCV13)			1 st dose	2 nd dose	3 rd dose		← -- 4 th dose -- →										
Inactivated poliovirus (IPV <18 yrs)			1 st dose	2 nd dose	← ----- 3 rd dose ----- →							4 th dose					
Influenza (IIV4)					Annual vaccination 1 or 2 doses								Annual vaccination 1 dose only				
Influenza (LAIV4)										Annual vaccination 1 or 2 doses		Annual vaccination 1 dose only					
Measles, mumps, rubella (MMR)					See Notes		← - 1 st dose - →					2 nd dose					
Varicella (VAR)							← - 1 st dose - →					2 nd dose					
Hepatitis A (HepA)					See Notes	2-dose series, See Notes											
Tetanus, diphtheria, acellular pertussis (Tdap ≥7 yrs)															1 dose		
Human papillomavirus (HPV)															See Notes		
Meningococcal (MenACWY-D ≥9 mos, MenACWY-CRM≥2 mos, MenACWY-TT≥2years)		See Notes												1 st dose		2 nd dose	
Meningococcal B (MenB-4C, MenB-FHbp)														See Notes			
Pneumococcal polysaccharide (PPSV23)													See Notes				
Dengue (DEN4CYD; 9–16 yrs)														Seropositive in endemic areas only (See Notes)			
Range of recommended ages for all children Range of recommended ages catch-up vaccination Range of recommended ages for certain high-risk groups Recommended vaccination can begin in this age group Recommended vaccination based on shared clinical decision-making Not recommendation/ not applicable																	

Range of recommended ages for all children

Range of recommended ages catch-up vaccination

Range of recommended ages for certain high-risk groups

Recommended vaccination can begin in this age group

Recommended vaccination based on shared clinical decision-making

Not recommendation/not applicable

Notes: Measles, mumps, rubella (MMR): during international travel infants age 6–11 months 1 dose before departure; revaccinate with 2-dose series at age 12–15 months (12 months for children in high-risk areas) and dose 2 as early as 4 weeks later. Hepatitis A: during international travel infants age 6–11 months 1 dose before departure; revaccinate with 2 doses, separated by at least 6 months, between age 12–23 months. For detailed information on Meningococcal Vaccination: MenACWY-D, MenACWY-TT, MenB-4C, MenB-FHbp) and Pneumococcal vaccination see <https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html#note-mening>.

KEY CONCEPTS

Current Areas of Vaccine Need

- Human immunodeficiency virus (HIV)
- Lyme disease
- Malaria
- Powassan disease
- Rocky Mountain spotted fever
- Universal coronavirus (SARS-CoV-1, MERS, SARS-CoV-2)
- Tuberculosis (TB)
- Tularemia
- Zika

Present and Future Challenges

A few specific challenges facing those involved in vaccine research and discovery are highlighted below to illustrate the ongoing needs in the area of public health.

A Vaccine for HIV. The development of an HIV/AIDS vaccine has long been recognized as a top HIV research global priority at the US National Institutes of Health. Strong and simple treatments for those who are living with HIV infection are now available and have even been rolled out to developing countries. It has been shown that treatment-as-prevention, wherein the viral load is lowered to an undetectable level by antiretroviral treatment of infected persons, results in a benefit to the infected patient and up to 96% reduction in HIV incidence in sexual partners.⁶²

More recently, antiretroviral agents have been tested globally and licensed in the United States as a once-daily pill (a combination of tenofovir and emtricitabine) for HIV/AIDS prevention in higher-risk individuals.⁶³ Known as pre-exposure prophylaxis (PrEP), this approach, in an idealized setting where resources and human adherence were not limiting, could have a truly dramatic impact on HIV incidence. However, to date, uptake has been low, and adherence has been a concern. A federal initiative, Ending the HIV Epidemic: A Plan for America,

which includes a plan to make PrEP medication available without cost for up to 200,000 people a year for 11 years, was announced in 2019 to help combat these issues and reduce the number of new HIV infections in the United States.⁶⁴

While the advances in HIV treatment, treatment-as-prevention, and PrEP have been significant, the numbers of new infections globally remain unacceptably high, with 1.7 million new infections in 2019 and a total of 38 million people living with HIV infection.⁶⁵ In the United States, progress on prevention of HIV infections through condoms, education, and evidence-based interventions plateaued new infections to ~36,400 in 2018 (<http://www.cdc.gov/hiv/library/reports/hiv-surveillance.html>).

The global need for an HIV vaccine remains. However, the scientific challenges have proven significant, and despite more than 30 years of major effort since the identification of the viral etiologic agent of AIDS in 1984, there is no approved HIV vaccine with proven protective efficacy. The majority of efficacy trials completed to date have not achieved protection of higher-risk vaccinated subjects relative to placebo recipients.⁶⁶ Additionally, in two of the trials (which tested replication-deficient adenovirus serotype 5 recombinant vaccine vectors expressing HIV Gag, Pol, and Nef but not Env), the studies were halted early with either concern over possible enhanced HIV acquisition in a small subset of participants or lack of prevention efficacy in the vaccine groups relative to the placebo groups.⁶⁶

Importantly, modest vaccine efficacy was observed in the RV144 efficacy trial reported in 2009.⁶⁷ Conducted by the US Army in collaboration with the government of Thailand. This 16,000-person study evaluated a prime-boost regimen of a non-replicating canarypox vector prime (expressing HIV Gag, protease, and gp120) followed by boosting with the same vector, plus a bivalent gp120 protein adjuvanted in alum. The RV144 regimen produced 61% protection in the first year post-vaccination and modest (31.2%) protection at 3.5 years post-vaccination.⁶⁷

This first evidence of human protection by an HIV vaccine proved that the development of an HIV vaccine may be possible and has re-energized the field. The US HIV Vaccine Trials Unit Network (HVTN), National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), US Army, and country-level and industry collaborators have formed the Pox-Protein Public-Private partnership (also known as P5) to plan an intensive series of follow-up human studies to confirm and fully investigate the important leads provided to the field by RV144.⁶⁸ One such follow-up efficacy trial of 5407 participants in South Africa (HVTN 702) was unfortunately not as successful as RV144. This trial was investigating a poxvirus vector and a bivalent gp120 protein adjuvanted with MF59, both modified to express clade C. The HVTN 702 trial was recently halted when the data and safety monitoring board (DSMB) found that the regimen did not prevent infection compared to placebo recipients.⁶⁹ Additional analysis is ongoing to discover the reason behind these discrepant outcomes.

A holy grail for HIV vaccines remains the discovery of a vaccine immunogen that induces broadly neutralizing, protective antibodies. Such antibodies occur naturally in up to 15% of chronically infected persons, usually after years of infection. Although seen in natural infection, no vaccine has been able to readily induce these broadly neutralizing antibodies in vaccinated humans. However, several broadly neutralizing monoclonal antibodies (bnAbs) have been isolated and cloned, and several have been tested for safety and pharmacokinetics in human trials. To date, these bnAbs have proven safe and

well-tolerated in both healthy and HIV-infected recipients.^{70–72} In viremic recipients who do not have resistant viruses present prior to infusion, receipt of either a single or combination of bnAbs results in a temporary decrease in circulating viral load, which typically rebounds once the serum levels of the bnAb lower below a protective concentration.^{73–75}

NIAID, through two of its HIV/AIDS clinical trials networks (the HVTN and the HIV Prevention Trials Network (HPTN)), is conducting two phase 2B efficacy trials of a broadly neutralizing monoclonal antibody, VRC01 (Clinical trials HVTN 703/HPTN 081 and HVTN 704/HPTN 085).^{70,75} The VRC01 efficacy trials (or AMP studies for antibody-mediated protection) are randomized, double-blind, placebo-controlled clinical trials. In the AMP studies, VRC01 was infused IV every eight weeks for 18 months at doses of 0 mg/kg (placebo), 10 mg/kg, or 30 mg/kg. While VRC01 was generally well-tolerated and demonstrated a favorable safety profile, it did not prevent acquisition of resistant viral strains. It did, however, protect against sensitive isolates, providing 75% protection over the 20-month trial to at-risk populations exposed to sensitive subtype B and C variants.

These results support what many experts suspected: rather than a single antibody, a combination of potent monoclonal antibodies targeting different epitopes on the gp120 envelope protein structure may be required to produce broad protection across a range of diverse subtypes. Combinations of two or three bnAbs are being evaluated in early-phase trials (NCT04173819, NCT04212091, NCT03928821).^{75a}

Improved Influenza Vaccines

The disease burden due to seasonal influenza A is significant, with the highest morbidity and mortality occurring in children, older adults, pregnant women, and persons with chronic medical conditions.⁷⁶ During an average year, seasonal infections result in an estimated 3 to 5 million severe cases and 291,000 to 645,000 influenza-associated deaths worldwide.⁷⁷ In the United States, it is currently recommended that all persons 6 months or older receive an annual influenza vaccine.⁷⁶ This recommendation serves to protect the vaccinated individual as well as those in the community who cannot be vaccinated themselves.

Influenza A and influenza B viruses are responsible for the majority of human infections. Multiple subtypes of influenza A are categorized based on the amino acid (AA) sequence homology within the viral surface proteins, hemagglutinin (HA), and neuraminidase (NA). So far, 18 HA and 11 NA subtypes have been discovered. Currently, two influenza A subtypes (H1N1 and H3N2) and two antigenically distinct lineages of influenza B (Yamagata and Victoria) co-circulate in humans,⁷⁶ with one strain of each represented in the quadrivalent seasonal vaccine developed each year.

Influenza is a segmented negative-stranded RNA virus of the Orthomyxoviridae family that lacks a proof-reading function in its viral polymerase and therefore mutates rapidly. These mutations result in an antigenic drift of the surface proteins, requiring an annual vaccine reformulation. Currently, licensed vaccines are produced in either embryonated eggs or cell culture and include inactivated influenza vaccines (IIVs), recombinant influenza vaccines, and live attenuated vaccines.⁷⁶ WHO issues a new vaccine strain recommendation for the vaccine each February, and vaccine manufacturers then race to produce the year's seasonal vaccine by late summer in order to be ready for the winter influenza season. There are multiple challenges and

needs with regard to this annual process of influenza vaccine prediction, production, distribution, implementation, uptake, and protection (Fig. 87.2).

Young children (particularly those between 6 months and 5 years of age) and older adults have a higher risk of severe illness during influenza infection. Children between 6 months and eight years of age should receive two doses of vaccine administered at least four weeks apart during the first season they receive vaccination for optimal protection.⁷⁶ Quadrivalent inactivated influenza vaccines (IIVs) are approved for all ages, while live attenuated influenza vaccines (LAIVs) should only be administered to children over 2 years of age, and quadrivalent recombinant influenza vaccines (RIVs) to children over the age of 4 years. For older adults, currently licensed vaccines provide relatively weak protection overall but remain an important public health measure. Immunosenescence is a large contributor to this reduced vaccine efficacy, resulting in increased disease susceptibility and severity. One solution to this challenge has been the approval of a high-dose vaccine, containing a fourfold higher dose of antigen, for a total of 60 mcg (compared to the standard 15 mcg) of each viral HA protein. This high-dose vaccine was shown to increase efficacy and was approved for use in older adults in the United States in 2009 (trivalent) and 2019 (quadrivalent).^{2,78} A vaccine formulated with the oil-in-water adjuvant, MF59, was approved for use in the United States and may increase immunogenicity

in older adults (<https://www.fda.gov/vaccines-blood-biologics/approved-products/fluad>).³

An ongoing issue with seasonal influenza vaccines involves the variable vaccine effectiveness for each viral antigen within the vaccine, which is partially dependent on the degree of match between the vaccine strains and the circulating strains. In order to allow manufacturers the six months currently required for egg-based vaccine production, the vaccine strains for each subtype and lineage must be selected in February of each year for the following season's vaccine campaign. The burden of annual revaccination of the entire population against a variable viral target is high, both logistically and financially. Furthermore, uptake of the annual seasonal influenza vaccine in the general population remains suboptimal. Over the past decade, considerable effort has been put into the development of universal influenza vaccines that would produce a broad immune response capable of protecting an individual against more antigenically drifted viruses and should ideally mean protection for more than one influenza season. A common approach to the rational design of such a vaccine involves selecting antigens in the more conserved regions of the virus, including the highly conserved HA stalk rather than the hypervariable HA head and other conserved internal proteins. Some of the universal influenza vaccine candidates are moving into early phase human safety and immunogenicity clinical trials, with the ultimate goal to improve or possibly supplant the current annual vaccination

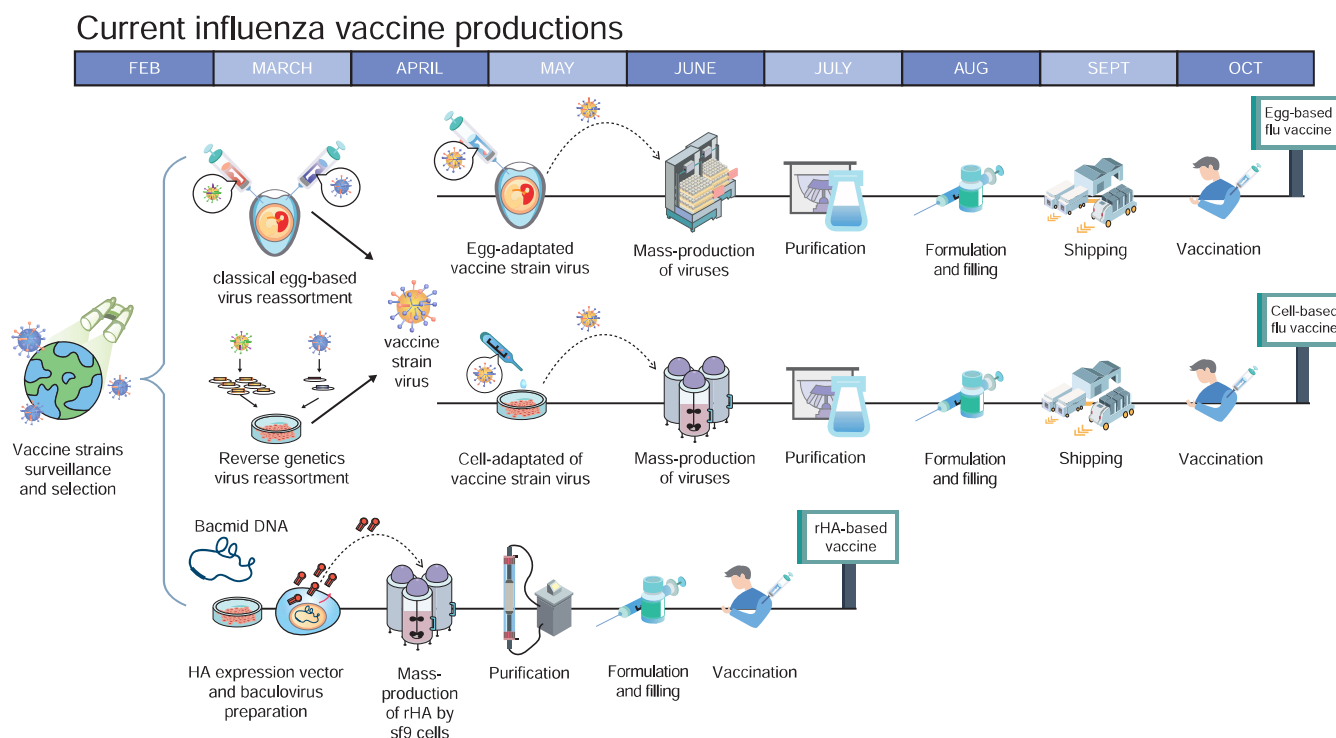


FIG. 87.2 Current Influenza Vaccine Productions. Timeline of current influenza vaccine production methods. Schematic overview of egg-based, cell-based and recombinant protein-based influenza vaccine production. Vaccine strains that match circulating influenza viruses for the upcoming flu season are selected by the World Health Organization (WHO) Global Influenza Surveillance and Response System (GISRS). High yielding vaccine strains for egg- or cell-based production are generated by either classic or reverse genetic reassortment. These adapted viruses go into mass production, either in embryonated eggs or MDCK cells with a production timeline of approximately 6 to 8 months. In recombinant hemagglutinin (HA) vaccines (rHA), the HA sequence is cloned into baculovirus and expressed by insect cells, significantly shortening production time. (Reproduced from Chen JR, Liu YM, Tseng YC, Ma C. Better influenza vaccines: an industry perspective. *J Biomed Sci.* 2020;27[1]:33.)