

Influenza Virus and SARS-CoV-2 Vaccines

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Seasonal influenza and the current COVID-19 pandemic represent looming global health challenges. Efficacious and safe vaccines remain the frontline tools for mitigating both influenza virus and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-induced diseases. This review will discuss the existing strategies for influenza vaccines and how these strategies have informed SARS-CoV-2 vaccines. It will also discuss new vaccine platforms and potential challenges for both viruses. *The Journal of Immunology*, 2021, 206: 2509–2520.

As highlighted by the current coronavirus-induced disease-19 (COVID-19) pandemic, the potential to respond rapidly to generate effective vaccines against emerging viruses is of critical importance. Since its establishment in 1948, the World Health Organization (WHO) has coordinated emergency responses to global health crises and pandemics (1). Although their efforts have been critical for controlling infectious diseases such as smallpox, HIV, and Ebola, their functioning primarily relies on the collaboration of United Nation member states. Unfortunately, after the 2009 H1N1 pandemic, the WHO concluded that the global community was not ready to control future pandemics (2). This concern is likely due to many factors, including the need to share genetic sequencing data, enhance the speed of vaccine design and development, and assemble the infrastructure to scale up vaccine candidate production and worldwide distribution. During the current COVID-19 pandemic, dissemination of data from rapid sequencing and identifying isolated strains of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has supported the generation of clinical vaccine candidates with unprecedented speed. The ability to respond so quickly is due in part to applying the knowledge gained from previous respiratory vaccine development, including influenza and other coronaviruses such as SARS and Middle East respiratory syndrome (MERS). This review describes lessons learned and challenges discovered from seasonal and pandemic influenza vaccine strategies that should inform the continued development of vaccines against the novel SARS-CoV-2.

Influenza viruses

Influenza viruses are enveloped negative-sense RNA viruses that cause acute respiratory diseases. Although influenza viruses are classified into type A, B, and C, only type A and B viruses are recognized as major drivers of human disease (3–5). Type A viruses are classified by the composition of the two major viral surface glycoproteins, hemagglutinin (HA) and neuraminidase. Type B viruses are separated into two distinct lineages characterized by their antigenicity (B/Victoria and B/Yamagata). Currently, the circulating seasonal influenza viruses consist of A (H1N1), A (H3N2), and the two lineages of influenza B viruses. Although there are no known pandemic strains in circulation currently, the seasonal A (H1N1) virus is the remnant of the viral strain that caused the 2009 “swine-flu” pandemic.

The challenges of influenza vaccines. A major challenge in influenza vaccine design stems from the constant evolution of influenza viruses. The error-prone activity of influenza viruses’ RNA-dependent RNA polymerase causes mutations in the viral surface proteins, allowing for escape from immune memory recognition (4, 6–8). The accumulation of these point mutations is referred to as genetic or antigenic drift and is largely responsible for seasonal influenza epidemics. Antigenic drift results in the generation of unique viruses that are closely related because of these small mutations. Influenza A viruses can also undergo a process referred to as antigenic shift that can create novel pandemic strains (3, 6, 9). Antigenic shift results from combining genetic composition from two or more strains of influenza viruses, which leads to the abrupt generation of a novel strain. This occurs in type A viruses that not only infect humans, but have strains that can infect or have reservoirs in other wild and domesticated species such as birds, pigs, and horses. Although not occurring frequently, if a virus that primarily infects nonhuman hosts either reassorts with a human virus or gains the ability to infect humans, novel and potentially highly virulent strains can arise, leading to pandemics (10–13). Since the notorious 1918 “Spanish flu,” there have been only three other recorded cases of novel pandemic influenza strains, including H1N1, H2N2, and H3N2 (Table I).

Other major challenges for influenza vaccine include the low efficacy against relevant circulating viral infections and limited

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Abbreviations used in this article: ADE, Ab-dependent enhancement; COVID-19, coronavirus-induced disease-19; CVV, candidate vaccine virus; HA, hemagglutinin; MERS-CoV, Middle East respiratory syndrome CoV; PS, pulmonary surfactant; RBD, receptor-binding domain; S, spike; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WHO, World Health Organization.

Table I. Previous recorded influenza pandemics

Pandemic Year	Influenza A Subtype	Nonhuman Species of Origin	Estimated RO	Estimated Mortality Rate (%)	Total Estimated Deaths	References
1918	H1N1	Avian	1.2–3.0	2–3	20–50 million	(12, 13, 191, 192)
1957–1958	H2N2	Avian	1.5	<0.2	1–4 million	(11, 12, 19, 193)
1968–1969	H3N2	Avian	1.3–1.6	<0.2	1–4 million	(11, 12, 19, 193)
2009–2010	H1N1	Swine/avian	1.1–1.8	0.02	100,000–400,000	(2, 19, 25, 194)

RO, reproductive number.

duration of immunity. Despite the lack of a current pandemic strain, seasonal influenza still constitutes a major healthcare burden with about 5 million severe cases and 650,000 deaths annually worldwide (14). Vaccines serve as the primary preventative measure for seasonal influenza and are recommended for all healthy individuals older than 6 mo of age (15, 16). Unfortunately, the current influenza vaccines vary yearly in efficacy between 19–60% and only provide ~3–4 mo of protection (17, 18). This low efficacy is due in part to the high levels of antigenic drift found worldwide and the selection of candidate vaccine virus (CVV) strains based on predictions 1 y prior to the vaccine year (17, 19–22). Since 1948, the WHO has defined CVV strains based on collected global influenza surveillance data. Current seasonal influenza vaccine strategies are comprised of inactivated CVVs, live-attenuated CVVs, or recombinant HA proteins from CVVs to make trivalent vaccines or quadrivalent vaccines (Table II) (16). Trivalent vaccines target both subtypes of seasonal type A influenza and select either the Victoria or Yamagata lineage of type B influenza, whereas quadrivalent vaccines include both B influenza lineages (23). As opposed to seasonal influenza vaccines, development of pandemic vaccines relies less on multivalency and more on strong surveillance and preparedness strategies.

The threat of influenza pandemics. Influenza pandemics arise when transmissible novel viruses gain the ability to infect susceptible humans without effective therapeutics to control resulting disease or infection. Surveillance of zoonotic influenza viruses with pandemic potential is the first line of prevention against future pandemics (9). To assess pandemic potential, zoonotic influenza viruses are separated into subtypes that have caused previous pandemics and those that have the rare ability to infect humans. In the past century, only H1N1, H2N2, and H3N2 viruses have caused pandemics, making these HA proteins the first tier of targets for vaccines against future pandemics (Table I) (24). Clinical trials testing H1N1 pandemic

vaccines account for over 63% of all clinical trials for vaccine application against potential pandemic influenza strains, whereas the other two tier 1 viruses make up only 2% (Fig. 1A, Supplemental Table I). Tier 2 vaccine targets are defined by HA proteins from viruses that are known to have sporadically infected humans in the past (H5N1, H7N9, and H9N2). Although tier 2 viruses are not easily transmitted to humans, they can produce a very high mortality (30–60%) in humans that are infected with these viruses (25, 26). Controversial gain-of-function studies clearly demonstrate the pandemic potential of H5N1 in which substitution of as few as 3 aa allowed for aerosol droplet spread in ferrets (27, 28). Because of the high mortality and pandemic potential from H5N1, almost 24% of all pandemic influenza clinical trials focus on H5N1 vaccines (Fig. 1A, Supplemental Table I). The majority (~78%) of the pandemic influenza clinical trial candidates use more conventional vaccine formulations incorporating inactivated split virus, commonly used for season influenza vaccines as well as inactivated whole virus and inactivated subunit vaccines (Fig. 1B, Supplemental Table I). Although historically effective, inactivated virus vaccines rely on growing the virus in cell culture or after egg adaptation, which can be laborious compared with recombinant protein or genomic-based vaccines (29). Alternative vaccine formulations, such as genomic, recombinant subunit, or viral vector–based vaccines, can overcome this limitation and potentially improve the speed of generation of future influenza vaccines. Should a zoonotic influenza virus with pandemic potential gain the ability to infect humans, the continued development and stockpiling of successful vaccines against these viruses will promote rapid scale-up vaccination processes.

The design of universal influenza vaccines. We should strive to accomplish the ultimate goal for both seasonal and pandemic influenza vaccines in developing effective universal vaccines that generate broadly neutralizing Abs against all influenza viruses that infect humans. Broadly neutralizing influenza Abs were initially identified in patients postinfection or repeated seasonal influenza vaccinations (24, 30–60). Although vaccination to specifically elicit broadly neutralizing Abs still has not been clinically successful, clinical trials using passive vaccination through convalescent serum or treatment with broadly neutralizing Abs have shown promise against severe influenza infections (30, 52). Recent National Institutes of Health guidelines define a universal influenza vaccine as one that is 75% effective at protecting against all influenza A viruses for at least 1 y in all age groups to whom the vaccine is administered (61). Any additional protection, such as cross-protection against influenza B viruses, is considered secondary. Multiple strategies to generate universal influenza vaccines have been applied, and in general, these approaches focus on generating broadly neutralizing responses against evolutionarily conserved regions of the HA stalk (24, 25, 62). Alternative approaches using adjuvants to boost

Table II. Current influenza vaccines in the United States for 2019–2020

Name	Developer	Recommended Age
Inactivated trivalent (IIV3)		
Fluad	Seqirus	≥65 y
Fluzone High-Dose	Sanofi Pasteur	≥65 y
Inactivated quadrivalent (IIV4)		
Afluria Quadrivalent	Seqirus	≥6 mo
Fluarix Quadrivalent	GlaxoSmithKline	≥6 mo
Flucelvax Quadrivalent	Seqirus	≥4 y
FluLaval Quadrivalent	GlaxoSmithKline	≥6 mo
Fluzone Quadrivalent	Sanofi Pasteur	≥6 mo
Recombinant inactivated quadrivalent (RIV4)		
Flublock Quadrivalent	Sanofi Pasteur	≥18 y
Live-attenuated quadrivalent (LAIV4)		
FluMist Quadrivalent	AstraZeneca	2–49 y

Adapted from Ref. 16.

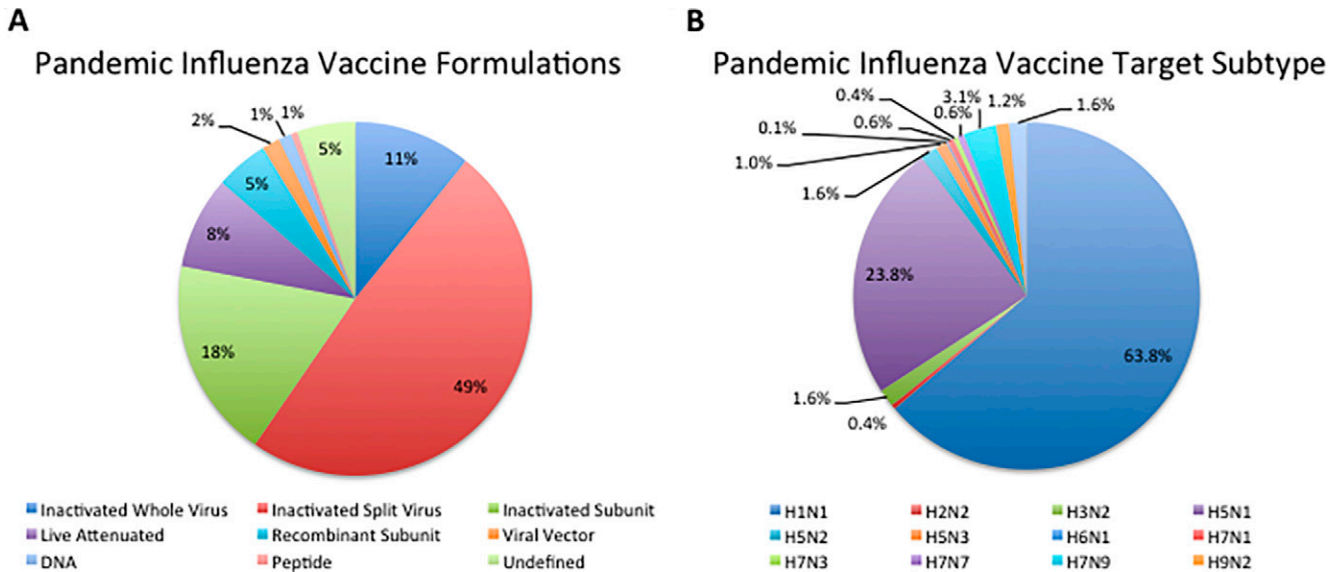


FIGURE 1. Summary of pandemic and potentially pandemic influenza vaccine clinical trials. Of 676 clinical trials tracked by the WHO, the frequency of (A) formulations used and (B) influenza subtypes targeted. Data adapted from Ref. 163.

vaccine efficacy also stimulate increased generation of broadly neutralizing Abs.

The adjuvants for a successful vaccine. Adjuvants can largely be categorized as either delivery systems or immune activators and often function in both arenas (63). The addition of adjuvants to vaccines has been shown to increase vaccine duration and efficacy through a variety of mechanisms (Table III). The choice of adjuvants is critically important to ensure proper immune activation and function. The most classical adjuvant added to vaccines consists of some variation of aluminum salts. Unfortunately, in the context of antiviral vaccines, these adjuvants are not highly potent and often lead to an undesired Th2 allergy-like immune response rather than the desired Th1 antiviral immune response (64, 65). Oil-in-water emulsions, such as MF59, AS03, and AF03, have assumed more prominence than aluminum salts, showing promise in clinical trials by increasing APC activation, B cell Ab production and antiviral T cell stimulation (66–72). Immune activators are molecules that specifically activate host immune responses through the sensing activity of pattern-recognition receptors (PRRs), such as TLRs or NOD-like receptors (NLRs), or consist of cytokines that can drive specific immune responses. Immune activators and Ags can also be delivered using nano- and microparticles to increase their effectiveness (73–88). Microparticles can be designed molecularly to mimic viral morphology using viral membrane components to create virus-like particles or using biomaterials to deliver cargo to specific cell types (63, 73, 75, 87, 89–93). These studies strongly highlight the benefit of targeted delivery of adjuvants. Previous work from our group has demonstrated that polymeric microparticles composed of acetalated dextran delivering cGMP-AMP, a potent inducer of the PRR stimulator of IFN genes (STING), resulted in a significant increase of both humoral and balanced Th1/Th2 responses to influenza HA (73). Another recent study developed a novel pulmonary surfactant (PS) biomimetic microparticle loaded with cGMP-AMP, referred to as PS-GAMP (89). Addition of PS-GAMP to a variety of monovalent and trivalent vaccines delivered intranasally led to impressive heterologous protection against both

type A and B influenza challenges. These reports are paving the way for developing potential universal vaccines. Combining broadly recognized vaccine Ags with strong immune-reactive adjuvants will hopefully lead to the development of universal influenza vaccines that protect against both seasonal and pandemic influenza strains.

The key issues to consider for future influenza vaccines. There are many challenges and potential risks in the development of seasonal, pandemic, or universal influenza vaccines. There are significant challenges to generating protective vaccine responses in elderly patients who tend to have weaker immune responses and who do not generate long-lasting immune memory (94, 95). Through the use of potent adjuvants, this limitation may be addressed and overcome. Abs that are cross-reactive to multiple strains of influenza, but not cross-protective, can also pose potential risks. One of these potential risks is Ab-dependent enhancement (ADE) (96). ADE occurs when nonneutralizing Abs bind surface viral proteins facilitating Fc-mediated uptake of the virus, leading to additional cellular tropism that could cause increased viral transmission and pathogenicity (97). For influenza, ADE has been shown to occur in pigs that were vaccinated against an H1N2 virus and then challenged with H1N1pdm09 virus (98). Future vaccine strategies generating broadly reactive Ab responses should be thoroughly tested to ensure benefit against a broad array of influenza viruses. Although exceptionally rare and the mechanism is still unclear, the 1976 swine influenza vaccine has been associated with activation of autoimmune disorders such as Guillain-Barré syndrome (99, 100). Potent adjuvants also often lead to flu-like symptoms that may dissuade people from getting vaccinated (101). However, in the context of pathogenic virus infections, the benefits of strongly protective vaccines far outweigh the risks, but safety is of paramount concern and should always be thoroughly evaluated.

SARS-CoV-2 pandemic

In late 2019, the novel coronavirus, SARS-CoV-2, gained the ability to infect humans (102–104). Early in 2020, it became clear that SARS-CoV-2 was highly transmissible through

Table III. FDA-approved clinical vaccine adjuvants (195)

Adjuvant	Composition	Mechanism	Vaccines	References
Aluminum	Amorphous aluminum hydroxyphosphate sulfate, aluminum hydroxide, aluminum phosphate, Alum	Activation of NLRP3 inflammasome and caspase-1 in DCs induces Th2 response	Anthrax, DT, DTaP (Daptacel), DTaP (Infanrix), DTaP-IPV (Kinrix), DTaP-IPV (Quadacel), DTaP-Hep B-IPV (Pediatrix), DTaP-IPV/Hib (Pentacel), Hep A (Havrix), Hep A (Vaqta), Hep B (Engerix-B), Hep B (Recombivax), Hep A/Hep B (Twinrix), HIB (PedvaxHIB), HPV (Gardasil 9), Japanese encephalitis (Ixiaro), MenB (Bexsero, Trumenba), Pneumococcal (Prevnar 13), Td (Tenivac), Td (Mass Biologics), Tdap (Adacel), Tdap (Boostrix)	(65, 196)
AS04	MPL + aluminum salt	Activates TLR4 on DCs, induction of cytokines and Ag-specific T cell activation	Cervarix	(197)
MF59	Oil-in-water emulsion composed of squalene	Rapid influx of CD11b ⁺ cells, upregulation of inflammatory cytokines and chemokines, recruitment of APCs	Fluad	(198)
AS01 _B	Liposome (containing MPL and QS-21)	Activates APCs expressing TLR4, stimulates cytokine and costimulatory molecules production, promotes Ag-specific Ab responses, and stimulates CD8 ⁺ T cells	Shingrix	(199, 200)
CpG 1018	Cytosine phosphoguanine, synthetic DNA	Activates TLR9 in DCs and B cells, induction of cytokines and Ag-specific T cell activation	Heplisav-B	(201)
No adjuvant			ActHIB, chickenpox, live zoster (Zostavax), MMR, meningococcal (Menactra, Menveo), rotavirus, seasonal influenza (except Fluad), single Ag polio (IPOL), yellow fever	(195)

ActHIB, Haemophilus b conjugate vaccine; Alum, potassium aluminum sulfate; DC, dendritic cell; DT, diphtheria toxin; DTaP, diphtheria-tetanus-pertussis (adolescent); FDA, Food and Drug Administration; Hep A, hepatitis A; Hep B, hepatitis B; Hib, Haemophilus influenzae b; HPV, human papillomavirus; IPOL, inactivated polio; menB, meningococcal group B; MMR, measles, mumps, and rubella; MPL, monophosphoryl lipid A; Td, tetanus and diphtheria; Tdap, tetanus-diphtheria-pertussis (>11 y).

person-to-person contact and showed higher lethality in older adults (104, 105). Due in large part to the lack of widespread viral tracing and poor containment during the early months of this disease, the current SARS-CoV-2 pandemic has caused 111 million cases worldwide with nearly 2.5 million deaths at an overall mortality of ~2% [as of February 17, 2021 (106); Table IV]. Although the medical burden caused by SARS-CoV-2 is staggering, the rapid worldwide response by scientists and healthcare workers to understand the virus and its disease pathology has also been unparalleled. This rapid response accelerated developments of critical frontline therapeutics and vaccine strategies (107–113). The pace of these advancements was energized through the scientific understanding of previous coronavirus epidemics and decades of vaccine research.

The coronaviruses and associated diseases. Coronaviruses are enveloped positive-sense ssRNA viruses that can lead to a wide-range of diseases usually associated with respiratory infections

(114, 115). Although there are seven coronaviruses that are known to infect humans, the majority cause only mild respiratory disease in healthy individuals (103). However, in 2002, the initial SARS-CoV first demonstrated the pandemic potential of the coronavirus family with almost a 10% mortality rate of infection (116–119). Later in 2012, MERS-CoV emerged with estimated 34.4% mortality (115, 120). As with pandemic influenza strains, zoonotic viruses that gained the ability of person-to-person transmission were identified as the cause of the SARS-CoV and MERS-CoV epidemics (103, 116). Fortunately, because of international containment efforts, these two viruses only infected a limited number of people (estimated 8096 and 2494 infected individuals, respectively, for SARS-CoV and MERS-CoV). Unfortunately, in 2019, key enhanced transmissibility of SARS-CoV-2 above previous emerging coronaviruses made containment of the virus more difficult (121, 122). These challenges include the long viral incubation period (~14 d) of

Table IV. Key clinical features of coronaviruses and influenza viruses

	SARS-CoV-2	SARS-CoV	MERS-CoV	Influenza	References
Receptor target	ACE2	ACE2	DPP4	α 2,6-Linked sialic acid	(138, 140, 202, 203)
Target cell population	Nasal, respiratory, corneal, intestinal epithelial cells, and alveolar macrophages	Epithelial cells, macrophages, monocytes, and alveolar type II cells	Nonciliated bronchial and epithelial cells	Ciliated epithelial cells and alveolar cells	(139, 191, 204–208)
Incubation period (range)	2–14 d	2–10 d	2–15 d	1–4 d	(202, 205, 209, 210)
R_0	2.2–6.47	2.0–3.0	<1	0.9–2.1	(211–215)
Initial clinical presentation	Fever, dry cough, myalgia, and fatigue	Fever, chills/rigor, myalgia, dry cough, headache, malaise, and dyspnea	Fever, cough, and shortness of breath	Fever, malaise, headache, and cough	(216–219)
Affected age	Patients >65 y of age represent the majority of hospitalizations and higher rates of mortality	Higher rates or mortality in patients >60 y old compared with younger patients	Mainly reported in adults, with children rarely affected	For influenza A, children <2 y and adults >65 y have the highest relative risk	(169, 206, 220, 221)
Mortality	2–3%	11%	35.67%	<0.1%	(106, 215, 219, 222–224)

SARS-CoV-2 and the increased spread in patients prior to the onset of symptoms or in patients who remain asymptomatic (123, 124). In patients who develop symptoms, infection with SARS-CoV-2 leads to highly heterogeneous outcomes, including COVID-19. Although pathology caused by SARS-CoV-2 shares many similarities to infections with influenza and previous coronaviruses, it does vary in key clinical features (Table IV). The major clinical disease, COVID-19, is characterized by fever, cough, and shortness of breath. In severe cases, there is lower respiratory illness leading to acute respiratory distress syndrome and cardiac failure (104, 125–127). Other potential symptoms of SARS-CoV-2 infection that are still not fully understood and require further study include blood coagulation and neurologic and gastrointestinal symptoms (128–131). There is still critical need to continue developing therapeutics against SARS-CoV-2–induced pathology, but because of high virus transmissibility, elusive nature, and economic and physiologic burdens on infected individuals, vaccinations offer the best opportunity for overcoming the ongoing pandemic.

The design of SARS-CoV-2 vaccines. The ability to rapidly develop SARS-CoV-2 vaccines was largely predicated on the research of previous coronaviruses, influenza, and other vaccine strategies (116, 132–135). One of the first key predictions that guided multiple SARS-CoV-2 vaccine developments was the selection of a stabilized viral spike (S) protein as the best vaccine Ag (135–137). As seen previously with SARS-CoV and MERS-CoV, the S protein of SARS-CoV-2 is critical for viral cellular adhesion and entry (Table IV) (138–140). Although vaccination against the receptor-binding domain (RBD) of the S protein is sufficient to generate protective immunity, the stabilized whole S protein or whole virion as the vaccine target generates the best protection against rechallenge in animal models (115, 132, 135, 136, 141). Previous coronavirus vaccine research also indicates that SARS-CoV-2 vaccines should strive for generating strong neutralizing B cell humoral responses and antiviral T cell memory cellular responses (132, 135, 142–144). Although the Ag target is critical for protective immunity, the overall formulation dictates the generation of strong humoral and cellular immune responses.

SARS-CoV-2 vaccine formulation demonstrates a major paradigm shift in vaccine design compared with classical and pandemic influenza vaccines. Currently, there are already six

SARS-CoV-2 vaccines that have been approved for use by some countries, with more that are showing promise in late-stage clinical trials (Table V, Supplemental Table II). In the United States, all of the SARS-CoV-2 vaccines that are currently used are issued under emergency use authorizations by the U.S. Food and Drug Administration. Of the currently approved vaccines internationally, only the Sinopharm inactivated whole virus vaccine (BBIBP-CorV) uses a traditional vaccine formulation (145). The other currently approved SARS-CoV-2 vaccines generate S protein–specific immunity using either nonreplicating adenovirus vectors or delivery of mRNA in lipid nanoparticles (Table V). Importantly, based on phase III clinical trials, the currently approved vaccines are strongly protective, with efficacies ranging from 62 to 95% (146–155). It is important to point out that comparing the efficacies of various approved vaccines is not valid because these vaccines were tested for different clinical end points and at different times during the course of the pandemic and/or in different locales. Hence, vaccine candidates may show less efficacy if they were administered later when several viral variants have already circulated to infect test subjects or in countries such as Brazil or South Africa where variants have become prevalent. Nonetheless, the SARS-CoV-2 vaccines have generally shown good efficacy, especially in preventing hospitalization or death. This high efficacy is likely driven by the generation of good neutralizing Ab responses in combination with strong Th1 T cell responses (Refs. 146, 156–160; M. Meyer, Y. Wang, D. Edwards, G. R. Smith, A. B. Rubenstein, P. Ramanathan, C. E. Mire, C. Pietzsch, X. Chen, Y. Ge, et al., manuscript posted on bioRxiv, DOI: 10.1101/2021.01.25.428136; and A. B. Vogel, I. Kanevsky, Y. Che, K. A. Swanson, A. Muik, M. Vormehr, L. M. Kranz, K. C. Walzer, S. Hein, A. Güler, et al., manuscript posted on bioRxiv, DOI: 2020.2012.2011.421008). Although preclinical mRNA–based vaccines have been shown to generate strong immunity, these vaccines are the first clinically approved uses for this vaccine platform (161). According to the Milken Institute, 20% of the 248 SARS-CoV-2 vaccine candidates tracked are based on RNA- or DNA-based formulations (Fig. 2) (162). Viral vector–based vaccines, including adenovirus vectors, make up another 20% of vaccine candidates. This is vastly different from previous pandemic influenza vaccine formulations in which gene and viral vector candidates together comprised less than 3% of

SARS-CoV-2 Vaccine Formulations

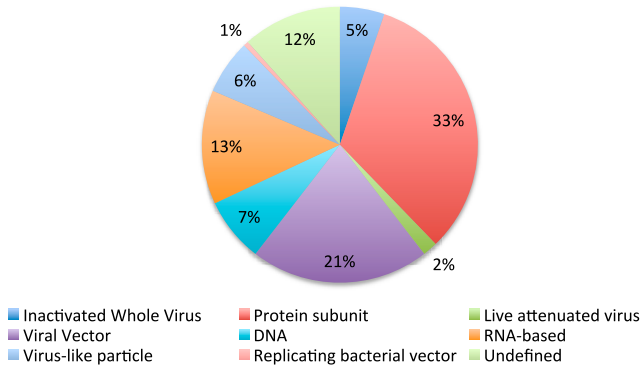


FIGURE 2. Formulation of 248 preclinical and clinical current SARS-CoV-2 vaccine candidates. Adapted from Ref. 162.

all vaccine formulations (Fig. 1B) (163). Furthermore, conventional formulations using attenuated whole virus, inactivated whole virus, or isolated components from inactivated whole virus that make up over 85% of pandemic influenza vaccines strategies are found in less than 10% of all SARS-CoV-2 vaccines. As the infrastructure to large-scale manufacturing and globally distribution of these novel vaccine platforms becomes established, these strategies can be used against current and future pathogens.

The challenges of SARS-CoV-2 vaccines. Despite the unprecedented success of the first wave of SARS-CoV-2 vaccines, there are still multitudes of challenges and unaddressed questions. The most immediate challenge is the manufacturing, distribution, and implementation of sufficient numbers of vaccines to achieve herd immunity. Distribution of the vaccines is made difficult because of refrigeration criteria of the mRNA vaccines. Further, only one that has been approved for emergency use requires a single dose, the others that are approved need two doses to achieve protective immunity (Table V). The ongoing development of single-dose and thermostable vaccines, along with global cooperation and coordination, should improve vaccine distribution and availability (Table V, Supplemental Table II). Next, increasing the understanding of the strength and duration of vaccine-induced immunity is required to develop vaccination schedules to maintain immunity. It is also still unclear whether the SARS-CoV-2 vaccines are effective at reducing transmission or will still allow for asymptomatic spread. Preliminary findings suggest that after vaccination with the mRNA-based SARS-CoV-2 vaccines, the viral burden in infected patients is significantly lowered (164). Further studies are needed to show whether this reduction leads to decreased transmission. Early studies also suggest that immunity generated after SARS-CoV-2 infection or vaccination should endure for over a year (157, 165–167). Although current data are promising, generation of robust immune responses may be more challenging in patients from high-risk groups with COVID-19 comorbidities, including elderly and immunocompromised patients and those undergoing immunomodulation or cancer therapy (168–172). Vaccine responses in elderly patients against other viruses have been shown to be impaired because of a process called immune senescence (170, 173). Immune senescence causes a variety of immune dysfunction, including the reduction in development of new T and B cells and leading to decreased vaccine-elicited adaptive immune responses. Alternatively, in patients undergoing cancer therapy or immunotherapy, vaccination may

not be recommended because of reduced vaccine efficacy or increase risk of adverse side effects (171, 174). Although achievement of herd immunity in the general public can help protect these groups, continued effort in SARS-CoV-2 vaccine development should also focus on protecting these high-risk groups (144, 175–179). Addition of immune modulators and adjuvants could be adapted for SARS-CoV-2 vaccines to improve protective responses in these high-risk patients (180). Importantly, early vaccination studies continue to prioritize inclusion of diverse populations, including wide ranges in age, race, and at-risk individuals (Refs. 146–148, 177–181, and F. Zhu, et al., manuscript posted on Research Square, DOI: 10.21203/rs.3.rs-137265/v1). Potentially, the most critical challenge to address is the ability of SARS-CoV-2 to mutate, leading to viral variants that may evade established immunity (182–185). Although the RNA reverse transcriptases of coronaviruses do have relatively good proofreading capability, they are known to undergo genomic mutations and recombination, promoting selection of viruses with improved viral fitness (186–189). It is likely that the SARS-CoV-2 variants will not be as prevalent as seasonal influenza variants, but it is too early to know if they will require similar seasonal vaccination strategies. Thorough surveillance for these emerging variants and generation of variant-specific vaccines should overcome this potential challenge. The latter is especially feasible because the mRNA vaccine formulations allow for a quick turnaround time for next-generation vaccines. Similar to influenza, the ultimate long-term goal is the development of universal coronavirus vaccines that protect against variants of SARS-CoV-2 and future emerging coronavirus species with pandemic potential.

Conclusions

Although it is exciting to witness the rapid evolution of pandemic vaccine strategies, the successes and failures of previous pandemic vaccine strategies should be considered for the continued development of effective SARS-CoV-2 vaccines as well as against future emerging pathogens. The emergence of highly pathogenic coronaviruses used to be relatively rare, but since 2004, three highly lethal and pathogenic coronaviruses have emerged. This disturbing increased frequency of pathogenic coronaviruses cannot be ignored. The major focus in pandemic influenza preparedness has centered on developing universal influenza vaccines that lead to cross-protection against all potentially pathogenic strains of influenza viruses. Finding antigenic epitopes that are conserved between divergent strains of coronaviruses may lead to the development of universal target Ags that can be used for universal coronavirus vaccines and, thereby, increase preparedness to combat future emerging coronaviruses.

In the last year, the many lessons learned and innovations made during the development of SARS-CoV-2 vaccines can be integrated into future influenza and emerging pathogen vaccination strategies. The ability to develop effective and safe vaccines quickly during an ongoing pandemic is paramount to curb the infection rate of these viruses. The accelerated timeline for SARS-CoV-2 vaccine development offers a good blueprint on how to prioritize both speed and safety for generation of future pandemic vaccines (190). Also, the continued understanding and establishment of manufacturing infrastructure for promising newly licensed vaccine platforms, including RNA-based vaccines,

Table V. Current approved and emergency use SARS-CoV-2 vaccine candidates

Developer	Vaccine	Phase III Efficacy	Platform	Previous Vaccine Use	Ag	No. of Doses (d)	Storage Temp.	Clinical Trial No.	References
Moderna/NIAID/ Lonza/ Catalent/ Rovi/ Medidata/ BIOQUAL	mRNA 1273	94%	RNA; lipid nanoparticle-encapsulated mRNA	SARS/MERS	S protein	2 (0, 28)	-20°C	NCT04283461, NCT04405076, NCT04470427, NCT04649151, NCT04677660, NCT04712110	(Refs. 151, 153, 157, 178, 225–228)
BioNTech/Pfizer/ Fosun Pharma/ Rentschler Biopharma	BNT162	95%	RNA; lipid nanoparticle-encapsulated mRNA		S protein and RBD	2 (0, 28)	-60 to -80°C	ChiCTR2000034825, EudraCT 2020-001038-36, EudraCT 2020-003267-26, NCT04368728, NCT04380701, NCT04523571, NCT04537949, NCT04588480, NCT04649021, NCT04713553	(Refs. 152, 155, 159, 160, 229–232 A. B. Vogel, manuscript posted on bioRxiv, DOI: 2020.2012.2011.421008; and U. Sahin, A. Muik, E. Derhovanesian, I. Vogler, L. M. Kranz, M. Vormehr, A. Baum, K. Pascal, J. Quandt, D. Maurus, et al., medRxiv, DOI: /10.1101/2020.07.17.20140533)
University of Oxford, Oxford Biomedica, Vaccines Manufacturing and Innovation Centre, Pall Life Sciences, Cobra Biologics, HalixBV, Advent s.r.l., Merck KGaA, the Serum Institute, Vaccitech, Catalent, CSL, and AstraZeneca/ IQVIA	AZD 1222 (formerly ChAdOx1)	62%	Nonreplicating viral vector	MERS, Influenza, TB, Chikungunya, Zika, MenB, plague	S protein	1	0 to -7°C	CTRI/2020/08/027170, EudraCT 2020-001072-15, EudraCT 2020-001228-32, ISRCTN15638344, ISRCTN89951424, NCT04324606, NCT04400838, NCT04444674, NCT04516746, NCT04540393, NCT04568031, NCT04686773, PACTR202005681895696, PACTR202006922165132	(146, 147, 154, 156, 158, 233, 234)
Gamaleya Research Institute	Sputnik V	92%	Nonreplicating viral vector		S protein	2	-18°C	NCT04436471, NCT04437875, NCT04530396, NCT04564716, NCT04587219, NCT04640233, NCT04642339, NCT04656613, NCT04713488, NCT04741061	(149, 235)
Beijing Institute of Biological Products/ Sinopharm	BBIBP-CorV	79%	Inactivated virus		RBD dimer	2	2–8°C	ChiCTR2000032459, ChiCTR2000034780, NCT04510207, NCT04560881	(145, 148)
Janssen Pharmaceutical Companies/ Beth Israel Deaconess Medical Center/ Emergent BioSolutions/ Catalent/ Biological E/ GRAM	Ad26.COV2-S (JNJ-78436725)	66%	Nonreplicating viral vector	Ebola, HIV, respiratory syncytial virus	S protein	1–2	2–8°C	EudraCT 2020-002584-63, NCT04436276, NCT04505722, NCT04509947, NCT04535453, NCT04614948, ISRCTN14722499	(236)

GRAM, Grand River Aseptic Manufacturing; NIAID, National Institute of Allergy and Infectious Diseases.

should improve rapid large-scale manufacturing against current and emerging pathogens. Adapting these vaccine platforms to influenza vaccines may further support improved influenza pandemic preparedness and vaccine efficacy. Increasing the diversity of clinically approved vaccine formulations is important for ensuring successful protection against current and emerging pathogens. This includes developing new biomaterials for safe and

effective delivery and incorporating adjuvants to cater specific robust immunity against both seasonal and pandemic viruses. It is important to consider the highly heterogeneous nature of the human population such that not all people react similarly to vaccine strategies. This increases the need to design and use a variety of vaccine platforms, thus increasing the options of protecting a wider panorama of the world’s population. Ultimately, the goals

of both influenza and coronavirus vaccines should be to elicit strong herd immunity and, if at all possible, to eradicate lethal strains of these viruses from the human population.

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