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Current vaccine strategies against SARS-CoV-2: Promises and challenges

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In the years since the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic began and spread across the globe, lessons have been learned about the challenges and opportunities that a pandemic brings to humankind. Researchers have produced many vaccines at unprecedented speed to protect people, but they have also been cognizant of the challenges presented by a new and unexpected infectious disease. The scope of this review is to examine the path of vaccine discovery so far and identify potential targets. Here, we provide insight into the leading vaccines and their advantages and challenges. We discuss the emerging mutations within the SARS-CoV-2 spike protein and other issues that need to be addressed to overcome coronavirus disease 2019 (COVID-19) completely. Future research is needed to develop a cheap, temperature-stable vaccine providing long-term immunity that protects the upper respiratory tract. (J Allergy Clin Immunol 2022;150:17-21.)

Key words: *Approved vaccines, variants of concern, SARS-CoV-2, COVID-19, preclinical vaccines, side effects, vaccine hesitancy, vaccine strategies*

Abbreviations used

COVID-19:	Coronavirus disease 2019
FCGRT:	Fc gamma receptor and transporter
OWS:	Operation Warp Speed
RBD:	Receptor-binding domain
S:	Spike
SARS:	Severe acute respiratory syndrome
SARS-CoV-1:	Severe acute respiratory syndrome coronavirus 1
SARS-CoV-2:	Severe acute respiratory syndrome coronavirus 2

The December 2019 emergence of severe acute respiratory syndrome (SARS) coronavirus 2 (SARS-CoV-2) in Wuhan, China, led to a pandemic that continues to be a threat.[1] Coronavirus disease 2019 (COVID-19), associated with the SARS-CoV-2, varies from mild respiratory illness to acute pneumonia and even respiratory failure. SARS-CoV-2 shares more than 70% genetic similarity with SARS coronavirus 1 (SARS-COV-1), which caused the 2003 outbreak.[2] Although SARS-CoV-1 was more pathogenic, SARS-CoV-2 has a higher reproductive number (R_0), indicating a much more efficient spread.[3] Studies have suggested that although both viruses bind to angiotensin-converting enzyme 2 (ACE-2), the structural differences in the surface spike (S) protein of SARS-CoV-2 enable a stronger binding to ACE-2 and greater efficiency at invading host cells.[4] Also, SARS-CoV-2 yields lower neutralizing titers than the SARS-CoV-1 infection.[5] Despite having proofreading capacity, SARS-CoV-2 can continuously evolve because of its high transmissibility and ability to evade the immune system, giving rise to variants of concern such as the Delta and Omicron strains. Thus, this evolving threat demands that we focus on the challenges facing vaccine research.

The rampant early spread of SARS-CoV-2 made it evident that only an effective vaccine would be able to control the pandemic. The perfect vaccine would be effective after a single inoculation, easy to administer, and stable at a wide range of temperatures, and it would prevent both disease and transmission. Of note, such a vaccine does not currently exist for any infectious disease that we face. The COVID-19 pandemic, however, promoted the rapid development of multiple vaccines against SARS-CoV-2 at an unprecedented speed. The process began in January 2020 and was greatly accelerated by government funding (via Operation Warp Speed [OWS]). The candidates were moved quickly through the preclinical and clinical development pipeline.[6] There are about 183 vaccine candidates, with 148 in clinical development and about 38 approved for use in different countries.[7] In the past, approval of conventional vaccines took about 10 years from the bench to the bedside, whereas the approval of COVID-19 vaccines was achieved in less than 2 years.

Why OWS chose certain vaccine platforms is still open for debate. Initially, the US government took the lead and invested several billion dollars in the development of 3 major vaccine platforms: (1) mRNA vaccines (Moderna and Pfizer), (2) replication-deficient live vectors (Janssen and AstraZeneca), and (3) SARS-CoV-2 S protein–based vaccines (Sanofi-GSK and Novavax). The reasons behind these decisions are not fully transparent and have led to other vaccine approaches being excluded prematurely. For example, the fear of vaccine-associated enhanced respiratory disease, which was observed previously with measles and respiratory syncytial virus inactivated vaccines, may have influenced regulatory bodies to drop certain platforms.[8] Contrary to these concerns, Corbevax, an alum

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This project was financed by a grant from NIH/NIAID 1R21 AI158044-01.

Disclosure of potential conflict of interest: M. J. Schnell and D. Kurup are coinventors of the patent application "Coronavirus disease (COVID-19) vaccine." The remaining author declares that he has no relevant conflicts of interest.

Received for publication March 23, 2022; revised May 3, 2022; accepted for publication May 4, 2022.

Available online May 23, 2022.

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0091-6749/$36.00

https://doi.org/10.1016/j.jaci.2022.05.008

hydroxide and CpG adjuvanted SARS-CoV-2 receptor-binding domain (RBD) vaccine, is now approved in 2 countries for use in children; with no serious side effects reported in the clinical trials.[9] To date, the clear front-runner in the race for an effective COVID-19 vaccine has been a new generation of genetic vaccines, the so-called mRNA vaccines (Fig 1, *A* and see Table E1 in the Online Repository at www.jacionline.org). OWS accelerated the human studies with Moderna mRNA vaccines. Interestingly, BioNTech, a German biotechnology company, had previously developed another mRNA vaccine and later partnered with Pfizer. The Pfizer/BioNTech vaccine was initially developed without government funding but was later included in the OWS portfolio for accelerated clinical trials even though the same mRNA platform had not shown much promise for several other infectious diseases, as previous human trials were not a success.[10] Still, both the Moderna and Pfizer mRNA vaccines demonstrated significant protection against COVID-19 in trials. In the short term, these mRNA vaccines certainly helped highly developed countries to manage the pandemic better than those countries without these vaccines. In the long run, however, the strategy of utilizing mRNA to protect the human population from COVID-19 needs to be revisited. mRNA vaccines are highly immunogenic thanks to the delivery system serving as a potent adjuvant, and they can be produced in large quantities. The mRNA vaccines performed better than the previously developed genetic vaccines, the so-called DNA vaccines, which are relatively easy and fast to make but lacked the high efficiency in immunity shown by the mRNA vaccine. However, although the mRNA vaccines helped to contain the pandemic in high-income countries, they were less successful in countries with fewer resources because of their high cost and the need for low-temperature storage facilities.[11] For instance, only 18% to 22% of the populations of Uganda and Ethiopia are fully vaccinated and revaccination of the population every 4 to 6 months in such environments is not feasible.[12] Thus, we still need cheaper, temperature-stable SARS-CoV-2 vaccines, considering that about 80% of the world's population lives in upper middle– to low-income countries.

The new mRNA technology can cause very unpleasant side effects which, although rarely serious or long-term, have soured a large portion of the population to such vaccines. The mild side effects include pain, redness, or swelling at the site at which the shot was administered and/or tiredness, headache, muscle pain, chills, fever, or nausea throughout the rest of the body; a few rare but severe side effects such as anaphylaxis can also occur.[13,14] Notably, there are concerns regarding the long-term immunity provided by these mRNA vaccines, which require a booster after 4 to 6 months.[15] It is almost certain that such immunization strategies will fail on account of the low compliance rate observed for influenza vaccination, which requires only yearly boosters.[16]

In addition to the mRNA and DNA vaccines, viral vector vaccines were also quickly developed during the pandemic. The first widely used viral vector COVID-19 vaccines were based on different replication-deficient adenoviruses (ie, the Johnson & Johnson [Johnson & Johnson/Janssen] and Oxford/AstraZeneca vaccines) or replication-competent viruses (eg, the Sputnik-V and CanSino vaccines). Adenoviruses are nonenveloped double-stranded DNA viruses that are most commonly responsible for mild, self-limiting respiratory and ocular infections in humans. Like the mRNA vaccine platform, the adenovirus vaccine platform is relatively new, although the vector has been used for gene therapy. The E1 and/or E3 viral genes enabling replication are deleted and replaced with the transgene of interest to generate a replication-incompetent adenovirus vaccine vector. Adenovirus vectors are relatively safe, as they do not integrate into the host genome (but remain episomal). They are more thermostable than mRNA vaccines, have broad tissue tropism, drive strong expression of the target antigen, and are readily scalable to meet the global demand. The vectors, which are based on the human adenovirus type 26 virus (which is rarely seen in the population) and the chimpanzee adenovirus vector, were used to circumvent the issue of preexisting adenovirus immunity, which affects the immunogenicity of the vaccine.[17]

Initially, the replication-deficient vectors showed some promise, but the immune responses were not as long-lived as envisioned. For example, waning immune responses were detected as early as 2 months after vaccination with the Johnson & Johnson/Janssen vaccine.[2] Although these vaccines are still used in some countries, they are no longer used in the United States. The widely used Oxford/AstraZeneca vaccine is not recommended in several groups of people on account of very rare but severe side effects (occurring in <1 in 10,000 people). The severe side effects include immune thrombosis associated with adenovirus vaccines, development of menstrual problems in women, capillary leak syndrome, and heart inflammation.[13,18] Although these vaccine-associated side effects are unpleasent and occasionally severe, observational cohort studies of patients with COVID-19 after discharge reported symptoms such as fatigue and dyspnea (39%), sleep disturbance (24%), chest pain (12%), and cough (11%) and had a readmission rate of 15% and a mortality rate of 6.7%,[19] suggesting that SARS-CoV-2 infections are far more deleterious. The immunity induced by the Oxford/AstraZeneca vaccine against SARS-CoV-2 is also likely limited. The development of attenuated pathogen vaccines based on the measles virus and vesicular stomatitis virus by Merck has been terminated on the basis of disappointing phase 1 immunogenicity results; however, these vaccines are still being pursued by other groups, and the results are pending.[20,21]

The other COVID-19 vaccines based on recombinant SARS-CoV-2 S proteins are virus-like particles containing all or part of the S protein, subunit protein vaccines, deactivated SARS-CoV-2 viral particles, or novel display platforms such as deactivated rabies virus[22,23] (Fig 1, *A*). Both of the subunit protein vaccines—that from Sanofi-GSK and that from Novavax—faced multiple delays and made it to market only very recently, even though they were generously funded (eg, $1.6 billion for Novavax). Additionally, "deactivated" or "killed" vaccines have a long history of safety and long-term efficacy, which can be lifelong. These platforms have provided some encouraging clinical and/or preliminary results, have minor side effects, and are likely to be more accepted by a larger section of the population because they have been successfully used previously for other vaccines. Whereas the "killed" vaccines provide better temperature stability, their developers still need to provide evidence for (1) manufacturing scalability, (2) long-term stability at 2°C to 8°C, and (3) long-term immunity without requiring regular boosting.

Studies of T-cell responses after natural infection and vaccination suggest that S protein–specific $CD4^+$ and $CD8^+$ T cells are dominant and detected the matrix and nucleoprotein responses to a lesser extent.[24] Despite extensive mutations and reduced neutralizing titers to heterologous SARS-CoV-2 strains, the T-cell responses following natural infection or vaccination were cross-reactive to heterologous SARS-CoV-2 strains and retained

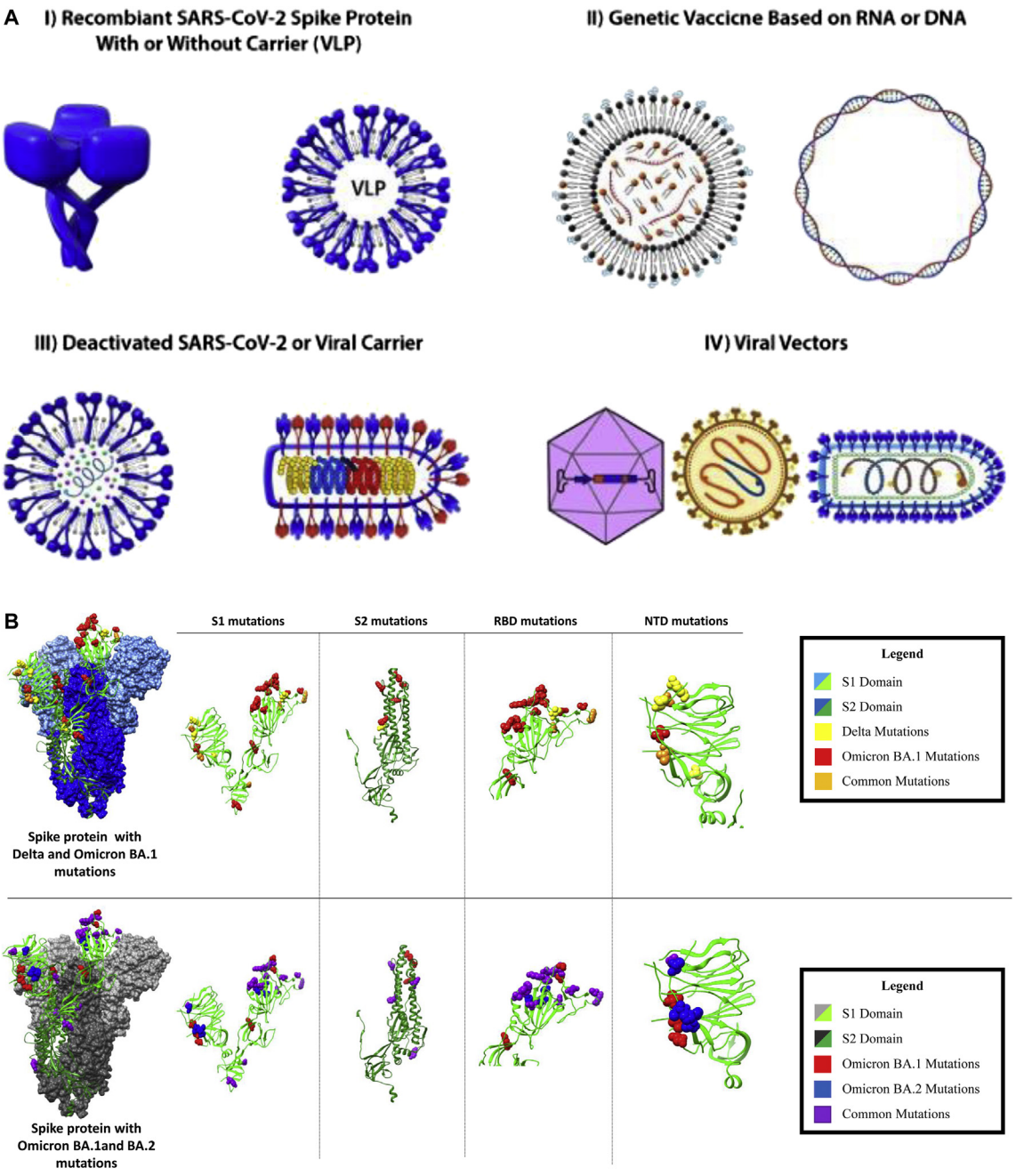

FIG 1. A, Different vaccine platforms currently utilized against COVID-19. *I,* The SARS-CoV-2 trimer is shown in blue in addition to a virus-like particle (VLP) with the trimer anchored within the VLP membrane. *II,* A lipid-based vehicle containing mRNA encoding the SARS-CoV-2 S protein and a DNA plasmid also encoding the S protein used for vaccination. *III,* Deactivated SARS-CoV-2 or viral vector–based particles are depicted. An example of the viral vector–based particle is the bullet-shaped viral particle based on the rabies virus; part of the SARS-CoV-2 S1 protein and its native glycoprotein are displayed. *IV,* Examples of 3 live viral vector vaccines based on adenovirus, measles virus, and vesicular stomatitis virus (*left to right*). **B,** Structure of the Omicron S protein with mutations highlighted. The 7T9J structure was used to illustrate mutations in the Delta, Omicron BA.1, and Omicron BA.2 variants. Two monomers are shown as surface topology with the third, highlighting mutations, displayed as a ribbon. S1 domains are displayed as light blue, gray, and green, whereas S2 domains are shown in dark blue, gray, and green. The Delta and Omicron BA.1 variants are compared with one another (*top panel*), and the Omicron BA.1 and Omicron BA.2 variants are compared with one another (*bottom panel*). Mutations that are unique (relative to the variant with which it is being compared) to the Delta, Omicron BA.1 and Omicron BA.2 variants, are shown as yellow, red, and blue, respectively (*depicted as spheres overlaid on the ribbon*). Mutations present in both the Delta and Omicron BA.1 variants are depicted in orange, whereas those common to the Omicron BA.1 and Omicron BA.2 variants are shown in purple. A list of the mutations used in generating this figure can be accessed in Table E2 (available in the Online Repository at www.jacionline.org).

up to 1 year after infection.[25,26] However, whether this retained T-cell immunity contributes to protection from severe COVID-19 remains to be determined.

An ongoing problem is the potential for emergence of novel SARS-CoV-2 variants that can escape the immune responses induced by the current vaccines or prior infection. Late 2021 saw the emergence of the Omicron variant, which has a great capacity to escape antibody neutralization[27] because it possesses S protein mutations both within common epitopes on the RBD and significant mutations away from the RBD, which could change the overall behavior of the protein[28,29] (Fig 1, *B*). The worldwide spread of the Omicron variant following its emergence and its high potential for breakthrough infections of vaccinated individuals[30] underscore the ability of SARS-CoV-2 to continue to mutate. It may potentially evade the high levels of population immunity achieved and threaten another such variant that we must be better prepared to control.

The mutations in the Omicron subvariant BA.2 seem to be the most recent set of mutations poised to become the next dominant strain. The subvariant BA.2 has already shown the capacity to reinfect individuals, even those recently infected with Omicron BA.1.[31] This is likely driven by several new mutations in the antigenic N-terminal domain and RBD,[32] as demonstrated in Fig 1, *B*. Breakthrough infections of fully vaccinated individuals have also been documented among those with BA.2 subvariants.[33,34] Although infections from the BA.1 lineage of Omicron have generally resulted in less severe disease than previous strains, preliminary data from France indicated that individuals with infection traced to the BA.2 lineage of Omicron has resulted in hospitalization at a significantly higher rate (approximately 4 times the rate associated with the BA.1 variant).[34] Clearly, the continued ability of variants to infect hosts that already possess immunity and recent data indicating a trend toward more severe disease in patients with the BA.2 variant are cause for continued concern. The recent explosion of the BA.2 subvariant BA.2.12.1, growing from 3% to 30% of the sequenced US caseload during April of 2022, underscores the fast-moving nature of this virus's mutation.[35]

We know that variants, including those with a high mutation rate that may or may not be controlled by the current vaccines, will continue to emerge. As with many topics related to COVID-19, we can only speculate as to what will happen in the future. The good news is that many of the mutants of SARS-CoV-2 did not spread as much as we anticipated and variants such as Omicron have mostly showed reduced pathogenicity. Of note, it is still unknown whether natural infection induces protective immune responses against proteins other than the S protein that may provide some additional protection. Some results indicate that vaccinating infected people induces better protection than does immunizing subjects twice.[36]

At this point, our opinion is that this new SARS-CoV-2 coronavirus will continue to mutate to a certain extent and will become a seasonal disease like the other 4 human coronaviruses and the seasonal flu. Thus, vaccines will still be needed, and development of a universal SARS-CoV-2 vaccine inducing long-lasting immunity is urgently required to protect vulnerable populations. Additionally, other vaccine platforms, such as live viral vector vaccines, have been developed. Despite these efforts to improve the COVID-19 vaccines, people with deep-rooted antivaccine opinions will continue to oppose vaccination for years to come, which creates other challenges for viral prevention. Lastly, many of the current vaccines provide excellent protection from disease, but none of the commercially available vaccines can prevent the spread of SARS-CoV-2; at best, they reduce the time during which an infected person can transmit the virus to others.[37,38] The more concerning fact is that immunized people can have an asymptomatic infection and put others—especially the immune suppressed and elderly—at risk.

Consequently, to address the shortcomings of intramuscular vaccination, many researchers are now working toward developing vaccines that target the respiratory mucosa. Recent preclinical assessments of intranasally delivered SARS-CoV-2 S protein–encoding chimpanzee adenoviruses have shown impressive mucosal immunogenicity as well as protection and reduced viral shedding in mice, hamsters, and nonhuman primates. Several studies have demonstrated that intranasal vaccination induces IgG, IgA, B-cell, and T-cell responses that can protect the upper and lower respiratory tract.[39-42] This may be due to the efficient transport of IgG to the surface of the lung but not the nasal passage owing to the lack of Fc gamma receptor and transporter (FCGRT) in the nasal epithelium. Therefore, vaccination and/or booster via the mucosal membrane, resulting in the induction of IgA, might be the solution, but the longevity of these responses is unknown. Mucosal vaccination has been successfully used with influenza virus but has failed in people with preexisting immunity. Therefore, preexisting immunity might be another concern for viral vectors. Several intranasal vaccines are now being tested in clinical trials.[43]

The need for additional booster shots has also driven researchers' efforts to develop a pan-coronavirus vaccine based on the influenza vaccine model, which may mean annual shots. The coronavirus family is a subfamily of orthocoronaviruses, and there are 4 different genera within the subfamily: *Alphacoronavirus* (which infects all mammals, including humans, causing cold-type symptoms, and most likely has bat origins); *Betacoranavirus* (Middle East respiratory syndrome, SARS, and SARS-CoV-2); *Gammacoronavirus*; and *Deltacoronavirus* (derived from ancestors in pigs and bird species). The genus *Betacoronavirus* has several sublineages: *Embecovirus* (lineage A; some of the common cold viruses), *Sarbecovirus* (lineage B; SARS and SARS-CoV-2 strains and variations thereof), *Merbecovirus* (lineage C; Middle East respiratory syndrome), *Nobecovirus* (lineage D), and a single variety of *Hibecovirus* (lineage E). Preclinical studies for developing pan-*Sarbecovirus* vaccines (targeting the RBDs or S protein from different sarbecoviruses) and pan-*Betacoronavirus* vaccines (targeting undisclosed antigens) are currently under way.[44]

In summary, many vaccines against COVID-19 are available, but none are perfect. The goal of vaccination is to decrease infections, hospitalizations, and mortality. Thus far, the perfect candidate—a vaccine that is cheap, is temperature stable, and provides long-term immunity (including in the upper respiratory tract)—has yet to be found.

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