Commentary

The Next Set of COVID-19 Vaccines: Leveraging New Development Platforms to Increase Access for More People Around the World

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ABSTRACT

The approval of the coronavirus disease 2019 (COVID-19) mRNA vaccines brought much optimism to efforts to end the pandemic. A recombinant adenovirus vaccine recently received emergency use authorization, and several other vaccines are likely to follow. These vaccines all use relatively new vaccine production platforms to produce the severe acute respiratory syndrome coronavirus 2 Spike protein. This review discusses how these platforms work, what advantages they offer, and the gaps that remain in public health efforts to control the COVID-19 pandemic. (*Clin Ther*. 2021;43:702–710) © 2021 Elsevier HS Journals, Inc. (*Clin Ther.* 2021;43:702–710.) © 2021 Elsevier Inc.

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INTRODUCTION

Currently, the coronavirus disease 2019 (COVID-19) pandemic has reached a new phase, which brings much cause for optimism. New cases are on the decline after a massive winter peak, schools and businesses are reopening in various parts of the country, and both versions of the mRNA vaccines are finding their way into many communities and settings for distribution. As of February 26, 2021, the Centers for Disease Control and Prevention reported that >70 million doses have been administered to >22 million adults receiving the 2-dose series.[1] However, there is still a long way to go before the United States and the rest of the world achieve the estimated threshold of 70% to 80% vaccinated for herd immunity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to control pandemic spread.[2] With the ongoing challenges of supplying both versions of the mRNA vaccines, it is welcome news that several other vaccine candidates are reaching the point of late Phase III testing and/or emergency use authorization (EUA) by the US Food and Drug Administration (FDA). The first review in *Clinical Therapeutics* covered the background of traditional vaccine approval, the EUA process, and details about the 2 mRNA vaccines.[3] This review focuses on 3 other versions of COVID-19 vaccines that represent new technologies for delivery of the SARS-CoV-2 Spike protein antigen: recombinant adenovirus 2 dose version (Oxford/AstraZeneca, Oxford, England/Cambridge, England), recombinant adenovirus 1 dose version (Janssen/Johnson & Johnson, Titusville, New Jersey/New Brunswick, New Jersey), and recombinant baculovirus expression system (Novavax, Gaithersburg, Maryland). They not only represent the potential for new populations who could receive vaccine but also present production and perception challenges as these versions become ready for distribution.

The Table summarizes the key information for the 5 SARS-CoV-2 vaccines discussed in this article and the prior review. To reiterate briefly, all versions of COVID-19 vaccines contain amino acid substitutions that lock the SARS-CoV-2 Spike protein in the prefusion conformation.[3] This change is required to generate a protective antibody response.

Oxford/AstraZeneca COVID-19 Vaccine

This version of the vaccine is a replication-defective chimpanzee adenovirus construct that encodes for

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Table. -SARS-CoV-2 Vaccine Formulations Summary

Manufacturer	Moderna	Pfizer/BioNTech	Oxford/AstraZeneca	Janssen/Johnson & Johnson	Novavax
Vaccine platform	mRNA	mRNA	Recombinant chimpanzee adenovirus	Recombinant adenovirus 26	Recombinant *Baculovirus* protein
SARS-CoV-2 antigen	Spike	Spike	Spike	Spike	Spike
No. of doses	2	2	2	1	2
Recommended dosing interval	28 d	21 d	12 wk	NA	21 d
Storage requirements	−20°C	−20°C updated	2°C to 8°C	2°C to 8°C	2°C to 8°C (−80°C initially)
Phase III trial efficacy overall estimates, %	95	95	70/60/10	66	89/50
Estimated efficacy against severe infection or hospitalization, %	100	100	NA	85/100	NA
Countries/sites for Phase III testing	United States	United States	United Kingdom/Brazil/South Africa	United States/Latin America/South Africa	United Kingdom/South Africa

NA = not applicable; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

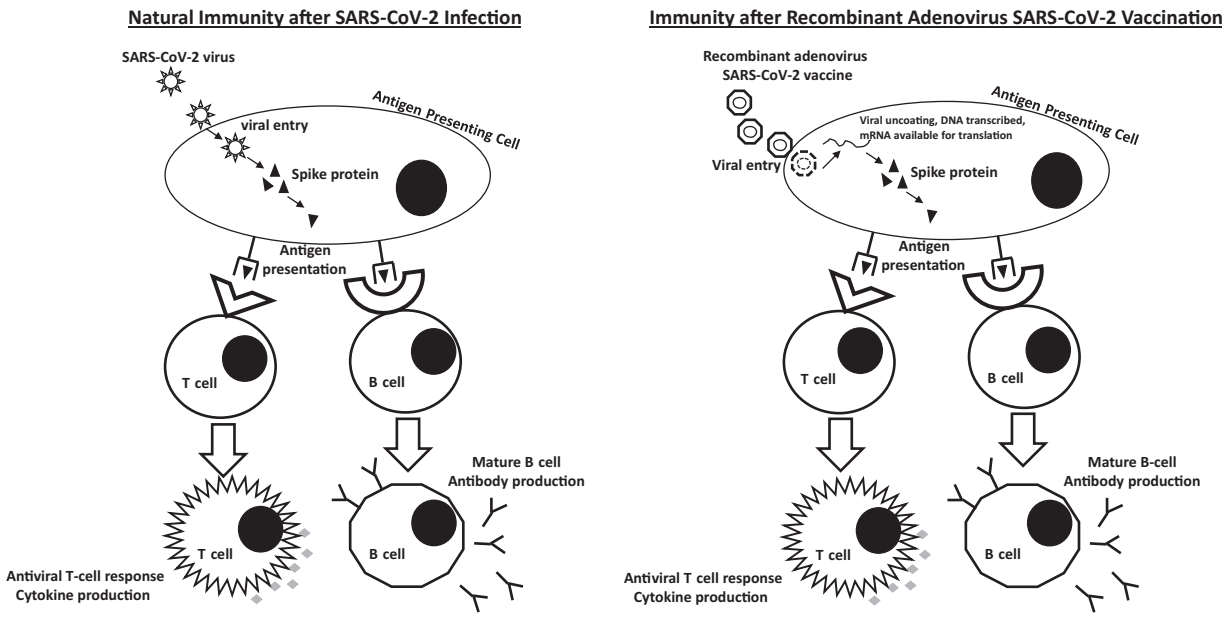

Figure 1. Natural immunity after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection versus immunity after adenovirus-vector SARS-CoV-2 vaccines. During viral infection, the SARS-CoV-2 virus is taken up by antigen-presenting cells. Individual proteins, such as the Spike protein, are presented to naive T cells and B cells to stimulate specific antiviral T cells and memory B cells to protect against future infection. With adenovirus vector vaccination, virus is taken up by cells via cell surface receptors, and after viral uncoating the RNA is translated in the cytoplasm to produce Spike protein. This Spike protein is then presented by antigen-presenting cells in the same way as during viral infection with the same downstream production of antiviral T cells and memory B cells.[3]

the SARS-CoV-2 Spike protein.[4] Recombinant virus expressing the Spike protein can be delivered to immune cells but cannot generate any new virus (Figure 1). This version was granted EUA in the United Kingdom on December 30, 2020, after release of Phase III trial results and in the midst of a surge in cases caused by a new variant with increased transmission efficiency.[5] As mentioned in the prior review, the primary purpose of this version of vaccine was to create a low-cost option (estimated $3 per dose) that could be produced and distributed to low- and middle-income countries around the world that have been effectively priced out of access to the mRNA vaccines.[6] In partnership with COVID-19 Vaccines Global Access (COVAX), the goal is to distribute up to 3 billion doses for global distribution.[7] In late February, Ghana was the first African country to receive doses for administration followed by Cote D'Ivoire.[8]

Despite the laudable goal, the clinical development of this vaccine has been far from uncomplicated. The vaccine candidate was evaluated in several different Phase I/II and Phase III studies across the United Kingdom, Brazil, and South Africa, and the data were combined to allow for a more robust estimate of efficacy.[4,9] The trials had some other changes as well: the initial 1-dose regimen was expanded to 2 doses; the initial dose was adjusted based on better methods to quantify viral quantity so some recipients received a low dose (half dose) for dose 1 and a full dose for dose 2, whereas most received 2 equal full doses, and the dosing interval was expanded from 28 days to up to 12 weeks for receipt of dose 2.[9] Adults 18 years and older were included in the trials, and the quadrivalent meningococcal conjugate vaccine was used in the control arm. Participants were asked to contact the study team if they developed symptoms any time during the study but were also asked to self-collect nasal swabs to monitor for asymptomatic infections. Of note, these studies were performed in the United

Kingdom and South Africa during a time when new SARS-CoV-2 variants had emerged.

The top line summary of the pooled results of these studies indicated an estimated 70% efficacy, but this figure does not capture many important details within the data.[9] First, there was a significant difference in estimated efficacy in the group who received the low dose for dose 1 (90% efficacy) compared with those who received the standard dose for both dose 1 and 2 (60% efficacy). The most plausible explanation for this result is that there is some degree of immunity against the vector that is generated by the higher first dose that may interfere with immunogenicity from the second dose. This immunity has been observed in gene therapy trials using adenovirus vectors.[10] Second, the efficacy against symptomatic infection was much higher than against asymptomatic infection (67% vs 27%). Third, there was higher estimated efficacy when the dosing interval between doses 1 and 2 was >6 weeks (65% vs 53%). A subsequent study found that when the interval between dose 1 and dose 2 was closer to 12 weeks the estimated efficacy increased to approximately 80%.[11] However, reduced efficacy was found in South Africa, where a new variant, known as 20H/501Y.V2 or B.1.351, generated concern. The data released as a preprint and reviewed in the *Financial Times* reported 10% protection against mild to moderate COVID-19 infection in a cohort of HIV-negative young adults.[12] Notably, these recipients received 2 standard doses 4 weeks apart, which based on the prior studies would have been a regimen that offered the lowest levels of efficacy. However, these caveats on the low-efficacy estimates were not raised in the preprint or the lay press, and South Africa has already announced they will procure additional vaccine from other companies as part of their national strategy against COVID-19.[13] The study evaluating dosing interval also reported 100% efficacy against hospitalization and severe COVID-19 infection.[11] Trials are under way in the United States, but they are being performed using the suboptimal dosing parameters of 2 standard doses and a dosing interval of 4 weeks (NCT04516746).[14]

This version of the vaccine would offer significant advantages. The storage requirements are quite forgiving: it can be kept at 2°C to 8°C for up to 6 months, which means it could be distributed very broadly to many office and non–health care settings around the world.[14] The very low production cost would rectify the tremendous inequity that currently exists between rich countries and the rest of the world. With >110 million global cases and >2.5 million deaths at the time of writing, a vaccine with 60% to 70% efficacy would have a tremendous impact on control of COVID-19 infections in low- and middle-income countries.[15]

What does this all mean for the Oxford/AstraZeneca COVID-19 vaccine as an option going forward? With the nuanced results and the need to modify the dosing regimen, the vaccine still needs additional study with an optimized dosing interval. It is very possible that a low-dose/high-dose combination spaced 12 weeks apart with an optimized SARS-CoV-2 Spike sequence that targets some of the mutations in the new variants could yield efficacy estimates that rival those of the mRNA vaccines. Given the low production cost and promise for global settings, it would be unjust to abandon this vaccine without fully studying every option to maximize its efficacy. If the product fails after attempts to increase efficacy, then a decision to move on to other options would be warranted.

Janssen/Johnson & Johnson COVID-19 Vaccine

This version of the vaccine is like the Oxford/AstraZeneca vaccine in that it uses a recombinant adenovirus vector expressing the SARS-CoV-2 Spike protein Fig. 1. This vaccine differs from the Oxford/AstraZeneca vaccine because this is not a chimpanzee strain but rather an adenovirus 26 strain that can circulate in its natural form. The adenovirus 26 platform was previously used to create a highly efficacious Ebola virus vaccine that was granted approval by the European Medicines Agency to allow for rapid distribution in the event of a future Ebola outbreak.[16,17] On February 27, 2021, this version of the vaccine was recently granted an EUA by the FDA after review of Phase III trial results.[18] Phase I/II studies found that this vaccine offered significant antibody levels and neutralization titers with only 1 dose.[19] This finding presents a tremendous advantage to quickly achieve protection across a population.

In addition to the single dose, there are some other practical advantages to this version of the vaccine. It is provided as a multidose suspension that does not need to be reconstituted, so it can simply be drawn up and administered. It is stable at conventional refrigerator temperature (2°C to 8°C) for long-term storage and for 6 hours after being drawn into a syringe and 2 hours at room temperature.[20]

Although a 2-dose Phase III study is still ongoing, the results of the 1-dose Phase III study were included in the FDA briefing document.[20] More than 40,000 participants were included, with approximately 14,000 being older than 60 years and just less than half having comorbidities. After excluding >4000 participants for testing SARS-CoV-2 positive by polymerase chain reaction and/or serologic testing, 39,300 were included in the per-protocol analysis. Because the trial was performed in the United States, Latin America, and South Africa, there was considerable racial and ethnic diversity: 17% reported as Black or African American race and >40% as Hispanic or Latino ethnicity. The overall vaccine efficacy against moderate to severe COVID-19 infection was 66% (173 cases in vaccinees vs 509 in placebo recipients), with virtually identical results in the 18- to 59-years-old cohort and >60-year-old cohorts. Efficacy was higher in the United States (72%) compared with South Africa or Latin America (64% and 61%, respectively). Sequencing of isolates from South Africa confirmed that 95% of cases were due to the prevailing variant strain, so the 64% efficacy should represent a real-world estimate of its performance. As the severity of infection increased, so too did the vaccine-induced protection: 85% against severe or critical COVID-19 (as defined by the FDA)[21] and 100% against hospitalization and life-threatening infection. There were 7 COVID-19-related deaths, and all occurred in placebo recipients. An interesting subanalysis included in this study was estimated efficacy against asymptomatic infection: only 12% to 22% within the first 29 days after vaccine but 59% to 74% after day 29. In all, these results support the overall efficacy of this vaccine. On the basis of these results, South Africa has paused its plans to administer the Oxford/Astra Zeneca vaccine and instead has moved forward with distributing the Janssen/Johnson & Johnson COVID-19 vaccine to their health care workers.[13]

For the near future, what will likely remain the biggest issue for this vaccine is limited supply. With the EUA issued, there are only a few million doses that will be distributed immediately, with a goal of 20 million before the end of March 2021.[22] Johnson & Johnson expects to supply more doses later in their promised window to fulfill their initial contracted total of 100 million doses by June 2021. Johnson & Johnson has announced partnerships with Sanofi and Merck to help enhance production.[23,24] Although Johnson & Johnson is one of the largest health care companies in the world, it has not been present in the vaccine market at all. A partnership with Sanofi, one of the largest global manufacturers of vaccines, should significantly increase their ability to deliver vaccine well into the future. Regardless of when the doses are ultimately delivered, it is clear that the Janssen/Johnson & Johnson COVID-19 vaccine will be an important part of the pandemic response going forward.

Novavax COVID-19 Vaccine

The Novavax vaccine is distinct from the Oxford/AstraZeneca and Janssen/Johnson & Johnson vaccines because it is composed of purified recombinant Spike protein.[25,26] The gene is inserted into a baculovirus vector expression system, which infects insect cells *in vitro* (Figure 2). Spike protein that is produced by these infected cells is collected, concentrated, and purified into antigen to be administered as a vaccine. The antigen is combined with a proprietary adjuvant that is derived from saponin to help increase immunogenicity with less antigen (called dose sparing).[26] Baculovirus expression systems are commonly used in scientific research to produce recombinant purified proteins. This technology was used previously to create a highly efficacious hepatitis E virus vaccine candidate,[27] and Novavax has used or is using this platform to create vaccine candidates against Middle-East respiratory syndrome, respiratory syncytial virus, and influenza.[26] When future vaccine supply is considered, it is important to note that the company has never had an FDA-licensed vaccine product.

Phase I/II studies with this vaccine candidate evaluated several different number of doses, antigen levels, and dose interval combinations.[28] These studies found that 2 doses of 5 μg and 25 μg combined with adjuvant administered 21 days apart offered antibody levels and neutralization titers that were robust and comparable to those found in convalescent serum from laboratory-confirmed COVID-19 recovered volunteers. The lower dose of 5 μg offered a much better adverse effect profile than the 25-μg dose and further allows the company to produce more doses of vaccine with less antigen. Phase III studies using this regimen of 2 doses of 5 μg 21 days apart have completed enrollment, 1 study with 15,000 participants in the United Kingdom and 1 study with 30,000 participants in the United States and Mexico.26

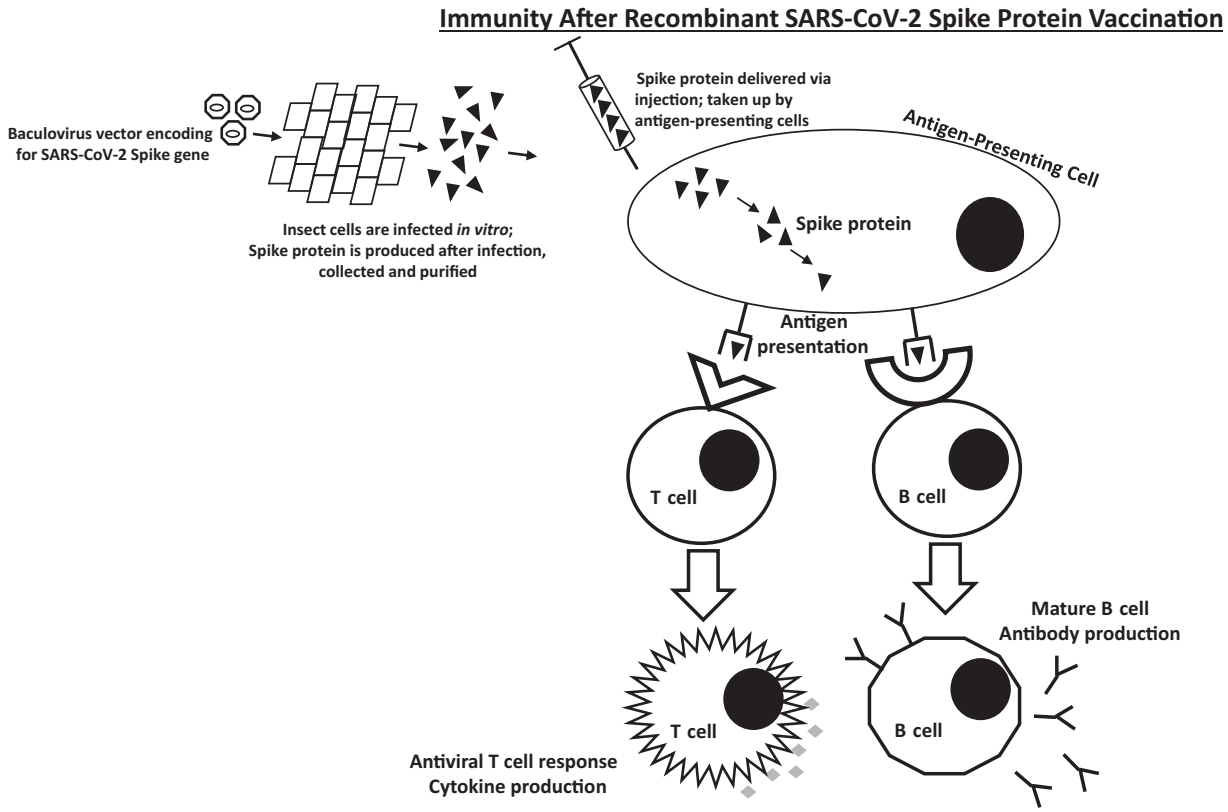

Figure 2. Immunity after recombinant severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein vaccines. Baculovirus vectors are cloned to contain the SARS-CoV-2 spike protein gene. Recombinant virus is used to infect insect cells *in vitro*, which ultimately leads to high level expression of the Spike protein. Protein is harvested from cellular material, concentrated, and purified before being packaged into vaccine doses. Vaccine is delivered by intramuscular administration, and Spike protein is taken up by antigen-presenting cells. This spike protein is then presented by antigen-presenting cells in the same way as during viral infection with the same downstream production of antiviral T cells and memory B cells.[3]

At the time of writing, some limited efficacy data were available from sources provided by the company.[25,26] In the UK Phase III study, the first interim analysis was based on 62 cases, 56 in the placebo group and 6 in the vaccinated group, which equates to an estimated vaccine efficacy of 89%.[25] Sequencing studies found that the UK variant was increasingly observed during the study, and the vaccine appeared to offer 85% protection against the B.1.1.7 variant. Interim data from the US and Mexico study are not yet available.

To their credit, Novavax amended their original Phase III study protocol to allow for crossover dosing of all participants.[26] This is the first trial to address the ethical concerns that many have expressed regarding the COVID-19 vaccine placebo arms. The crossover design maintains blinding while collecting safety and efficacy outcomes data. Participants receive extra inoculations but receive active vaccine as a volunteer.[29]

A separate Phase IIb study from South Africa is worth discussing because there are some very interesting observations to note.[25] There were a total of 4400 participants enrolled in this trial. Although the overall efficacy among all participants against any COVID-19 infection was <50%, the estimated efficacy in HIV-negative participants with mild, moderate, and severe disease was approximately 60%. Of the isolates identified in this study, >90% were the South African,

B.1.351 variant, so this level of protection is better than or comparable to those previously described vaccine candidates. This trial also included approximately 1500 participants with evidence of prior COVID-19 infection. Although it is not clear from the data available now whether this can be confirmed, it is hypothesized that these individuals were infected with isolates before the emergence of the new prevailing South African strain. The observations suggest that prior immunity may not fully protect against these new strains and that vaccine may have some role in optimizing protection. These data are quoted from the Novavax press release and not otherwise available for further evaluation, so some caution must be taken before fully accepting these claims.

Similar to the Janssen/Johnson & Johnson vaccine, this Novavax COVID-19 vaccine also has some practical advantages that make it appealing. It can be stored at 2°C to 8°C refrigerator temperature. In addition, it is provided as a liquid in 10-dose vials that can be drawn up and administered.[26] These attributes are well suited to existing vaccine infrastructure, which means this vaccine could be easily introduced into settings that currently offer vaccines and others that are designed to increase access to rural and/or underserved areas with populations at high risk of complications.

The biggest challenge is the scale up of production to meet demand. Novavax has been building their capacity during the last several months in anticipation of vaccine authorization, partnering with other US-based firms to assist with antigen and adjuvant production.[26] Novavax is contracted to deliver 110 million doses by the third quarter of 2021, but their estimated global capacity with new agreements may reach 2 billion doses per year. These are highly ambitious figures, but even delivery of a fraction of these doses will be a meaningful addition to global supply. There is specific mention of partnering with producers in India, but there is no specific mention of intent to distribute to low- and middle-income countries or suspending intellectual property claims to facilitate low-cost production.

Issues to Consider

Although the expected authorization of all these vaccines represent major steps in the progress toward ending this pandemic, there are still many issues that should temper enthusiasm. Domestic and global supply continues to be a major limiting factor. As mentioned in the previous commentary, the numbers needed to vaccinate to achieve the herd immunity estimate of 70% to 80% of the global population number in the billions of doses.[3] This unprecedented scale will require the expected supply of all the available vaccine plus many others not discussed. As pertinent as global supply is the issue of ongoing global inequity in vaccine availability. Rich countries continue to procure more and more vaccine doses, which effectively limits vaccine access for most of the rest of the world. COVAX is trying to address this inequity, but most countries will not receive significant doses of vaccine until well after 2021.[30]

Another significant challenge is that none of the 3 vaccines described in this commentary have been assessed in children younger than 18 years. Currently, the mRNA vaccines have both made significant progress in their pediatric studies of children 12 to 17 years of age, and the cohorts of younger children are now open for enrollment. On March 31, 2021, Pfizer/BioNTech released preliminary efficacy estimates in children 12-15 y.o of 100% protection against COVID-19. Reference: https://www.pfizer.com/news/press-release/press-release-detail/pfizer-biontech-announce-positive-topline-results-pivotal Accessed March 31, 2021. Children experience severe complications from COVID-19 and could benefit from vaccination. Although the overall burden of clinical disease is noted in elderly populations, the significant societal impact of COVID-19 on children has been overwhelming. In addition, unimmunized and often asymptomatic children likely serve as a source of transmission to those at risk of severe clinical disease. Advocates continue to make the case that pediatric studies should be an integral part of these Phase III trials, but thus far exclusion remains the rule.[31]

Creative approaches in study design, such as enrolling family members of all ages to receive vaccine doses, could have notably informed our understanding of both efficacy and effectiveness of vaccines. If the COVID-19 pandemic has a message for licensing and regulatory agencies, it is that we should aim for inclusion rather than exclusion of underepresented populations, including children, in early-phase clinical trials.

With several formulations of vaccine available, studies can begin to look at how administration of different formulations of vaccine could synergize with each other. The combination of a vectored

vaccine with a recombinant protein vaccine could offer superior protection than either alone. Those who received a prior mRNA vaccine could get a booster 1 to 2 years later with a recombinant protein or adenovirus vaccine that encodes a modified sequence to protect against newly identified mutations. Certain populations, such as children, older adults, or those with immunocompromise, may respond more robustly to certain formulations of vaccine than others.

CONCLUSIONS

With the introduction of several new formulations of vaccine, each representing a new innovation in vaccine design and production, optimism about control of the pandemic increases. However, challenges related to production, supply, and egalitarian distribution should temper this enthusiasm and reinforce the concept that this will need to continue to be a process that involves researchers, public health officials, industry partners, and regulatory agencies. In the meantime, the public needs continued vigilance adhering to public health measures of universal masking and social distancing to limit spread of the virus. Public health and industry representatives need to continue measures to maximize delivery of vaccine to the general population and research to determine which vaccines or combination of vaccines will provide long-lasting robust immunity against SARS-CoV-2.

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