

## VIEWPOINT

## Urgent Need for Next-Generation COVID-19 Vaccines

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**Despite the availability** of safe and effective vaccines, SARS-CoV-2 continues to circulate rampantly across the globe. Problems with vaccine access and hesitancy present throughout the pandemic are partially responsible. However, the seemingly ceaseless progression of increasingly transmissible variants, recently including BF.7 and BQ.1.1, presents a major challenge to medical interventions, particularly vaccines.

Attempting to address the continued genetic evolution of SARS-CoV-2, the US Food and Drug Administration authorized bivalent boosters (original plus BA.4/BA.5 Omicron variant) for the 2 available messenger RNA (mRNA) COVID-19 vaccines to address the waves of disease leading to hospitalization and death. These updated vaccines may also reduce the amount of symptomatic disease and associated health care use. However, introduction of these bivalent boosters likely only represents a temporizing measure until variants emerge that necessitate additional booster vaccination or modification of the current generation of vaccines.

The existing COVID-19 vaccines have had a profoundly positive effect during the pandemic, reducing both hospitalization and death. However, those at risk of severe outcomes from COVID-19, especially older individuals, have required booster vaccination even to

the development of a distinctly improved generation of SARS-CoV-2 vaccines offering longer protection with greater scope.

Based on experience to date with COVID-19 and other vaccines, a variety of approaches to the development of new vaccines will need to be explored by academic and industrial researchers and sponsors, as well as government agencies. One potential model for approaching such development was used successfully at the beginning of the pandemic when Operation Warp Speed evaluated numerous global vaccine types and focused on advancing several promising candidates, knowing full well that most would ultimately not be found to meet the criteria set forth for a safe vaccine with adequate efficacy.<sup>2</sup> Such focused effort, along with technical and financial resources, will likely be required to overcome the significant challenges intrinsic to efforts to develop a vaccine having the needed extent and duration of protection.

Developing the next generation of vaccines addressing SARS-CoV-2 will be demanding. This work will almost certainly require more than simply making incremental modifications on the current generation of vaccines. Although experience with the mRNA vaccine platforms has enabled authorization of updated versions of vaccines without large clinical trials, when more significant modifications are made to a vaccine, the clinical effects are often unexpected. Biological properties that may plausibly have beneficial effects often have unanticipated consequences. Therefore, unless correlates of protection that are strongly associated with duration of protection against COVID-19 can be identified, it is likely that rather than relying on immu-

nobridging to infer vaccine effectiveness, large randomized clinical trials similar to the initial trials of the currently authorized or licensed vaccines for COVID-19 will be required to ascertain the effectiveness of these new vaccines.

Simply updating the existing vaccine constructs with new variant sequences or even making trivalent or quadrivalent vaccines covering several variants is not likely to provide the depth and breadth of protection needed to interrupt viral transmission during a prolonged period. It is also not at all clear from well-controlled clinical trials that administering existing vaccines by the intranasal route (as some countries have already even approved) will provide truly meaningful benefit over the existing generation of COVID-19 vaccines. Such limitations were recently illustrated by the disappointing results with a viral-vectored vaccine administered intranasally in an early-phase clinical trial.<sup>3</sup>

## Serious consideration therefore needs to be given to the development of a distinctly improved generation of SARS-CoV-2 vaccines offering longer protection with greater scope.

maintain this level of protection. The need to repeatedly vaccinate at-risk populations, combined with the documented emergence of a new dominant SARS-CoV-2 variant approximately every 3 to 4 months, presents a public health dilemma.<sup>1</sup> Continuing along the current path of the generation and administration of variant-specific vaccine boosters is inadequate as a long-term strategy for addressing COVID-19 in populations globally.

There is also a risk that eventually a variant will emerge that will escape the protection provided by the current generation of vaccines against severe disease. Experience with SARS-CoV-2 infection to date in older individuals indicates that higher antibody titers tend to correlate better with prevention of severe COVID-19. Therefore, older individuals may be at risk for becoming the initial group most susceptible to such novel variants that lack adequate antibody coverage. Serious consideration therefore needs to be given to

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However, the situation is far from hopeless because there are other approaches to future COVID-19 vaccine development currently under investigation, including potentially effective means of achieving improved mucosal immunity with or without intranasal administration. These approaches might include, among many other methods, targeting S protein viral sequences that are immutable, immunogenic, and accessible to neutralizing antibodies; including other targets from the virus such as portions of the membrane, envelope, or nucleocapsid proteins; targeting conserved or occluded (structurally hidden) epitopes using nanoparticles of randomly arrayed receptor binding domains; and developing vaccines based on T-cell receptor constructs that specifically recognize the SARS-CoV-2 RNA-dependent RNA polymerase.<sup>4,5</sup>

So what would define success for these new vaccines? To truly represent a significant advance in this area, the protection provided by vaccination would need to apply across a wide range of potential variants that might emerge. In terms of the actual level of effectiveness, the minimum expectations for such a vaccine might be adopted from the criteria used in the search for an acceptable "universal" influenza vaccine. The National Institute of Allergy and Infectious Diseases defines the threshold for influenza vaccine as at least 75% effectiveness in preventing influenza-like illness, achieving durable protection that lasts at least 1 year, and suitability for use in all age groups.<sup>6</sup> Aiming even further, the vaccines would ideally not only protect against hospitalization, death, and symptomatic disease leading to increased health care use but would also

reduce viral transmission. Even using the criterion for success of a moderate 40% to 60% reduction in transmission is predicted to have a notable positive impact on outbreak control.<sup>7</sup>

The continued adverse effects of SARS-CoV-2 on individuals and populations necessitate the urgent development of the next generation of vaccines. The adverse effects wrought by SARS-CoV-2 extend far beyond the acute complications of COVID-19 to post-COVID-19 conditions. Achieving success in developing improved vaccines will obviously be a major challenge, given all that we have learned to date about this virus, the human response to infection, and the immune correlates of protection after vaccination. However, an attempt to produce vaccines that lead to broad long-lasting immunity is clearly needed. Additionally, although reducing viral transmission is a difficult objective, the potential benefits to global public health are profound enough to merit acceptance of the challenge. Particularly, if immunity that reduced disease transmission could be elicited by a relatively inexpensive, easily administered vaccine stored at room temperature, a much greater fraction of the world's population could be readily immunized, perhaps slowing the emergence of troubling variants.

What we learn as we address the challenges posed by SARS-CoV-2 and COVID-19 about virology and immunology, along with the accompanying advances in technology and manufacturing that will come from developing the next generation of vaccines, may broadly benefit public health during our current era of constantly emerging and reemerging infectious diseases.

#### ARTICLE INFORMATION

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