VIEWPOINT

Approaches for Optimal Use of Different COVID-19 Vaccines
Issues of Viral Variants and Vaccine Efficacy

John P. Moore, PhD
Weill Cornell Medicine, Cornell University, New York, New York.

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The efforts of the Biden administration to accelerate rollout of COVID-19 vaccines are enabling more adults in the US to be vaccinated each week. As of February 28, 2021, an estimated more than 48 million people have received at least 1 vaccine dose. Provided enough people are vaccinated, the US might be able to transition back toward prepandemic life at some point this year. However, one scenario that could adversely affect the vaccine program is the further evolution and spread of viral variants that are resistant to vaccine-induced neutralizing antibodies. It is prudent to discuss possible strategies to minimize the potential effects of this problem, and other scenarios for maximizing the benefit of available and future vaccine supplies.

The viral variant problem became prominent at the end of 2020. Two categories of variants have different implications for vaccine efficacy. The first category involves variants that arise when RNA viruses like SARS-CoV-2 replicate in people. One selection pressure on the virus is simply to infect human cells more efficiently and maximize the replication of its genome. A more fit and transmissible virus will spread more rapidly in a population. This happened during spring 2020 when the D614G variant became the dominant strain worldwide. The same phenomenon is occurring now with the B.1.1.7 strain that was first detected in the UK. The B.1.1.7 strain is more infectious and is projected to soon dominate the US pandemic. But neither the D614G variant nor the B.1.1.7 strain is notably resistant to vaccine-induced neutralizing antibodies, and most researchers have substantial confidence that these variants will not affect the efficacy of the present generation of vaccines.[1,2]

The second category involves variants that are more concerning, represented by the B.1.351 and P.1 lineages that emerged in South Africa and Brazil, respectively. These viruses have sequence changes in key positions suggesting that they arose under neutralizing antibody selection pressure within people infected with SARS-CoV-2. Unusual variants have been seen when the virus replicates at high levels for prolonged periods in immunocompromised individuals.[3] Even though what happens in such people is not identical to the environment in vaccine recipients who become infected, several similarities warrant consideration.

Whether neutralizing antibodies are induced by infection or vaccination, a strong neutralizing antibody response suppresses virus replication and a weak response does little to suppress replication, but neutralizing antibodies that have intermediate potency are thought to cause the virus to evolve and create ways to escape the constraint on its ability to replicate.[4,5] The combination of a high virus replication rate within an individual (a high viral load) and a suboptimal level of neutralizing antibodies is the exact environment in which resistant viruses are considered likely to emerge and spread.[3,4] To the extent possible, this scenario should be avoided in a vaccine program. In laboratory-based studies, the B.1.351 variant was found to be partially resistant to neutralizing antibodies induced by 2 doses of the Pfizer messenger RNA (mRNA) vaccine, the Moderna mRNA vaccine, and the Novavax protein vaccine.[1,2] In 2 reports, single-dose Pfizer vaccine serum antibodies could not neutralize B.1.351 at all.[2] The extent of B.1.351 resistance varies between studies but in 1 case it is quite troubling.[2] At present, most scientists active in this area are reasonably optimistic that the efficacy of the mRNA vaccines will not be substantially compromised by the B.1.351 and P.1 variants, but there is a clear need for a definitive, national testing program to determine the properties of virus variants. Neutralizing antibodies induced by the AstraZeneca adenovirus vaccine had very low activity against the B.1.351 variant and the vaccine was ineffective at protecting against this strain—a serious warning sign about the problems resistant viruses may pose.[6]

Are there possible strategies to minimize the emergence of additional and perhaps more resistant or infectious variants? For maximal efficacy, the Pfizer, Moderna, and Novavax vaccines are known or widely thought to require 2 doses. Although neutralizing antibodies can be detected after the first vaccine dose, their titers are strongly boosted by the second dose.[7,8] Accordingly, the vaccines are less effective during the interdose period than after the second dose. But there may be more value to the second dose than simply increased efficacy. When people are infected after the first dose but before the second dose, the virus can replicate in the setting of a suboptimal level of neutralizing antibodies, a situation in which resistant variants may emerge.[4] The intersection between virus replication and host antibodies underpins the current recommendation of a short interval between vaccine doses, which is national policy in the US but not in the UK. A recent troubling development is the detection in the UK of a new variant of B.1.1.7 containing the E484K substitution in the S-protein that is considered a hallmark of neutralizing antibody resistance. The sooner each person receives the stronger protection conferred by the second vaccine dose the better both for individuals and for the population.

The Johnson & Johnson 1-dose adenovirus vector vaccine has now received Emergency Use Authorization from the US Food and Drug Administration. This vaccine is easier to ship and store but it is less effective than the Moderna, Pfizer, and Novavax 2-dose designs. Johnson & Johnson/Janssen is also testing a 2-dose version of the vaccine that seems likely to provide stronger and perhaps more sustained protection, but this randomized clinical trial (RCT) (NCT04436276) is months away from completion.

Corresponding Author: John P. Moore, PhD, Weill Cornell Medicine, Cornell University, 1300 York Ave, New York, NY 10065 (jpm2003@med.cornell.edu).

Should the 1-dose Johnson & Johnson vaccine be considered as simply an alternative to the stronger Pfizer and Moderna vaccines (and the Novavax vaccine if that one is also approved)? Similar to the interdose period for the 2-dose vaccines, there may be a concern about resistant viruses arising when a significant number of Johnson & Johnson vaccine recipients become infected with SARS-CoV-2, particularly if the efficacy of the single dose wanes over time. One way to minimize that risk might be to restrict the use of the Johnson & Johnson vaccine to only younger people (perhaps those aged <40 years). The rationale is that COVID-19 is much more likely to be mild or asymptomatic in younger adults than in older adults. Lower severity infections may be associated with less viral replication. The less the virus replicates, the less likely vaccine-resistant viruses will develop. To confirm or refute this scenario, it should be possible to generate data on viral loads (using quantitative assays) for infected vaccine recipients of different age groups.

Another concern is whether a significant number of people will refuse to receive a vaccine that is less effective than the already-approved mRNA vaccines. Although public health authorities and clinicians will recommend that people accept whatever approved vaccine is offered, media reports from the UK and Europe indicate that some people have resisted receiving the AstraZeneca vaccine and prefer the mRNA vaccines. Careful messaging will be important particularly if the AstraZeneca vaccine is approved in the US.

Combining different vaccines is another possible approach that might improve overall vaccine flexibility and performance, which could be tested in small-scale RCTs. The higher efficacy reported for the Russian Sputnik V 2-component adenovirus vaccine (compared with the AstraZeneca 1-component design; both vaccines require 2 doses) suggests the possibility that antivector immunity compromises the efficiency of a second, identical adenovirus dose.[9] In their current formulations, the 3 adenovirus vaccines involve different combinations of adenovirus variants; the Sputnik V vaccine uses Ad26 for the first dose then Ad5 for the second dose, the AstraZeneca vaccine uses ChAdeno then ChAdeno, and the Johnson & Johnson vaccine uses Ad26 (then would use Ad26 in the 2-dose version). To overcome any problem involving antivector immunity, using a mRNA vaccine or protein vaccine to boost the first dose of the Johnson & Johnson or AstraZeneca adenovirus vectors could possibly be more effective than giving a second dose of the same adenovirus.

All leading vaccine companies are now redesigning their S-protein components to counter new variants, particularly B.1.351. Although it is unknown whether, when, and what additional variants might arise in the future, the E484K sequence change may represent a common solution as the virus adapts to neutralizing antibody–selection pressures. Appropriately designed animal or human studies are needed to assess whether something called the "original antigenic sin" applies. In that scenario, a redesigned vaccine preferentially boosts only the original neutralizing antibody response rather than eliciting a new set of antibodies that are intended to target the new virus variant. Knowing whether the original antigenic sin is or is not a problem would substantially inform future vaccine-dosing strategies if virus resistance worsens to the extent that vaccine booster immunizations are a necessary countermeasure.

Another issue with significant implications involves what happens when a mRNA vaccine is given to a person who has recovered from COVID-19. Small-scale studies have shown that a single mRNA vaccine dose rapidly boosts neutralizing antibody titers to very high levels, perhaps rendering the second dose redundant in this special circumstance.[10] Considering the number of people in the US who have had COVID-19, there is a potential to save tens of millions of vaccine doses. Although logistically this would be a major challenge, the French government has already adopted this policy. A related issue is that the mRNA vaccines appear to trigger strong (although short-lived) adverse effects (such as headaches and mild fever) in people who have previously been infected with COVID-19. One potential solution to the adverse effect problem might be to use the Novavax protein vaccine (if it is approved) to boost antibody levels in patients who have recovered from COVID-19, particularly for younger individuals. This vaccine seems to elicit fewer adverse effects than the mRNA vaccines but had comparable efficacy in a UK phase 3 trial. However, data from carefully designed clinical trials are needed to address these issues and inform the best decisions.

Hundreds of millions of additional doses of several COVID-19 vaccines will be available in the coming months. The vaccine companies and the federal government should work together to explore evidence-based approaches to maximize the value of this national resource.

ARTICLE INFORMATION

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Correction: This article was corrected on March 10, 2021, to remove the words "or previously infected" from the second sentence in the third paragraph.

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Editor's Note: Although preprints are rarely included as references in *JAMA* articles, in the midst of the COVID-19 pandemic some of the information in this article is based on rapidly developing and emerging science that is only available as preliminary communications on preprint servers.

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