VIEWPOINT

SARS-CoV-2 Vaccines and the Growing Threat of Viral Variants

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Multimedia

In November 2019, a bat coronavirus made its debut in the human population. Since that time, the virus has continued to adapt, resulting in a series of viral variants. The question that the world faces in early 2021 is whether these new variants will escape recognition by vaccine-induced immunity.

Protection against coronavirus disease 2019 (COVID-19) is mediated in large part by an immune response directed against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike (S)-protein. The S-protein is responsible for virus-cell binding and is the target for virus-neutralizing antibodies (NAbs). Although this is not strictly proven, most vaccine researchers believe that NAbs induced by vaccination are protective against COVID-19. NAbs bind to the S-protein at a few sites, usually in or near the receptor-binding domain (RBD); in doing so, NAbs prevent the virus from attaching to the ACE2 receptor on human cells.

Variants in the S-protein that increase the amount of virus shed from an infected person or that increase its affinity for the ACE2 receptor are likely to increase virus transmission, an important problem in the context of a pandemic. Furthermore, the same or similar alterations can change the shape of the S-protein and impair or even destroy NAb binding sites. Hence, by extrapolation, vaccine efficacy might be compromised.

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These "escape mutations" typically arise when the virus is put under selective pressure by antibodies that limit but do not eliminate viral replication. Under these conditions, the virus might then find a way to escape this pressure and restore its ability to reproduce more efficiently. The scenario of virus evolution in the face of suboptimal immunity is one reason extending the interval between the first and second dose of a SARS-CoV-2 vaccine might be problematic.

Evolutionary biology is now occurring across the globe. The first major shift in the properties of SARS-CoV-2 took place early in the pandemic—around March and April 2020—when the original strain was replaced worldwide by a new variant called D614G.[1] The relevant mutation in this variant, which is located in the S-protein, has been shown to increase the replication efficiency and transmissibility of the virus.[2] Although this variant did not escape recognition by NAbs, it was a warning of what could happen.

In August 2020 another variant started to spread in the UK (where surveillance for such events is particularly thorough), and its contribution to the pandemic in that country increased rapidly from November 2020 through January 2021. Often called the "UK strain," but more formally known as B.1.1.7, this variant has now been detected in many countries, including the US. The key sequence change in the S-protein is called N501Y, which again appears to increase the transmissibility of SARS-CoV-2, although in a manner subtly different from D614G. Regarding protection by vaccination, however, again fortunately, the location of the N501Y change makes it unlikely to affect most of the NAb binding sites on the RBD.[3] For example, recently released data show that serum samples from the recipients of the Pfizer-BioNTech and Moderna mRNA vaccines are equally effective at neutralizing viruses that contain or lack the N501Y change.[4,5]

A more transmissible variant now circulating in southern California, CAL.20C, has an RBD sequence change called L452Y that is thought to act similarly to N501Y.[6] Its sensitivity to vaccine sera remains to be determined.

There is now, however, a more troubling new variant identified in South Africa, the N501Y.V2 variant (or B.1.351). A close relative to N501Y.V2 with similar properties has now also been identified in Brazil (P.1), but much less is known about this variant. The N501Y.V2 strain has many more sequence changes than both the D614G and B.1.1.7 variants, and those sequence changes are more worrisome because they are located in or close to the RBD; these sequence changes also affect another NAb target, the N-terminal domain.

The number and positioning of these mutations immediately raised concerns among vaccine researchers. New data show that those concerns were not misplaced. Rockefeller University researchers have shown that the relevant N501Y.V2 sequence changes within the RBD modestly reduce the efficiency with which mRNA vaccine-induced antibodies neutralize test viruses in the laboratory.[7] In addition, a National Institutes of Health study now shows that NAbs induced by the Moderna mRNA vaccine are about 6-fold less active against the N501Y.V2 (B1.351) strain.[5]

It remains unclear whether the reduction in the neutralization sensitivity of the N501Y.V2 strain to vaccine-induced antibodies is enough to seriously reduce vaccine efficacy. First, mRNA vaccines also induce virus-specific helper T cells and cytotoxic T cells, both of which might be involved in protection against

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challenge. Also, the mRNA vaccines, in particular, induce such a strong NAb response that there could be enough "spare capacity" to deal with reductions in the sensitivity of the variant to NAbs. In other words, N501Y.V2 (and the related virus from Brazil) may be less sensitive to NAbs, but not to an extent that will cause widespread vaccine failure. However, vaccines that appear to induce lower levels of NAbs, such as the inactivated vaccines developed in China and India, may be less effective. It is too early to know how the replication-defective simian or human adenovirus vector-vaccines (Johnson & Johnson/Janssen's, AstraZeneca's, and the Russian "Sputnik V") or the adjuvanted purified protein vaccines (Novavax and Sanofi/GSK) might be affected. Much work is now being performed worldwide to better understand how these different vaccines are affected by the N501Y.V2 and related variants. An important clue should emerge when several phase 3 vaccine efficacy trials now ongoing in South Africa are completed. Will the increasing dominance of N501Y.V2 in that country affect how well these vaccines protect the trial participants? Time will tell.

In addition to avoiding recognition by vaccine-induced immunity, variants have also become less susceptible to neutralizing monoclonal antibodies (nMAbs). The N501Y change in the B.1.1.7 variant, for example, is sufficient to almost ablate the activity of several nMAbs, and the South African team's study shows that almost all of the nMAbs tested against N501Y.V2 were now ineffective.[8] The nMAbs that are approved by the Food and Drug Administration to treat SARS-CoV-2 infection need to be carefully assessed against all these new variants.

Given the rise of these viral variants, several steps should be taken.

First, SARS-CoV-2 viruses must be immediately isolated and characterized from individuals who have been fully vaccinated but are nonetheless admitted to the hospital with COVID-19. This would likely be the first sign that variant viruses are becoming resistant to vaccine-induced immunity.

Second, the US should create and maintain an active sequencing and surveillance system to identify these variants quickly once they arise. While the UK has been excellent in this regard, the US and much of the rest of the world has not. International cooperation is essential to do this properly.

Third, it would be of value to create a central repository of serum samples from people in the US who have been immunized with SARS-CoV-2 vaccines. This resource would enable researchers to test their neutralizing capacities against any new variants as soon as they are identified. In this way, it will not be necessary to depend on pharmaceutical companies, who have limited quantities of serum samples generated from phase 3 trials, to do these studies. A central repository should include samples representing all the approved vaccines, as well as those still in phase 3 trials, to enable gauging both the depth and breadth of neutralization resistance.

Fourth, it is essential to reduce the global spread of new variants, particularly N501Y.V2 and its related Brazilian variant. While it is likely that these viruses are already present in the US, the more often they are reintroduced, the more likely they will make it into a superspreader event, with very serious consequences for wider spread.[9]

Fifth, the designs of the mRNA and replication-defective adenovirus vaccines can be adjusted to accommodate the key sequence changes present in the new variants. The initial stages of this process are fairly straightforward and can be accomplished rapidly.

Sixth, like those that have circulated throughout 2020, the new variants are not spread by aerosolization in a manner similar to measles virus nor do they travel long distances. Wearing masks, physical distancing, and applying common sense can prevent their spread.

ARTICLE INFORMATION

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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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