Two More Vaccines Found Effective, but Less So Against New Variants

Last week both Novavax and Johnson & Johnson reported data from Phase III trials of their COVID-19 vaccine candidates. Both were effective at preventing disease and will be valuable tools in controlling the pandemic, but the results were more nuanced than previous efficacy results for Pfizer/BioNTech's and Moderna's mRNA-based vaccines. This was largely because both Novavax and Johnson & Johnson tested their vaccines in the context of emerging viral variants in both the U.K. and South Africa.

The B.1.1.7 SARS-CoV-2 variant that was first identified in the U.K. is associated with increased transmissibility. Another variant, known as 501Y.V2 or B.1.351, is now predominant in South Africa. In laboratory studies, the 501Y.V2 variant has been shown to escape from neutralizing antibodies, raising concerns about how well COVID-19 vaccines will perform against this variant (see the interview with Penny Moore, below). These concerns were substantiated by the recently reported results of the Novavax and Johnson & Johnson trials.

The U.S. company Novavax reported that their protein-based vaccine was 90% effective at preventing symptomatic COVID-19 disease in its Phase III efficacy trial involving more than 15,000 volunteers in the U.K., where the B.1.1.7 variant has become predominant. Meanwhile in a Phase IIb trial of Novavax's vaccine in South Africa, efficacy was only 49% amongst the entire study population, and 60% in volunteers who were not infected with HIV.

Results from Johnson & Johnson's Phase III trial showed that a single shot of their human adenovirus-based vaccine developed at Janssen Pharmaceutical Companies was 66% effective at protecting against moderate to severe cases of COVID-19, and 85% effective overall in preventing severe cases of disease, including complete protection against hospitalizations and deaths from COVID-19 in all regions.

"In my view, the best news from the latest vaccine trials is that the efficacy was high against severe disease, hospitalization, and death in the Johnson & Johnson trial in South Africa," says Marc Lipsitch, a Professor in the Department of Epidemiology at the Harvard T.H. Chan School of Public Health. "This suggests that existing vaccines can still have major effects on the most severe outcomes, even with the variant."

However, efficacy did vary geographically. At 28 days post vaccination with the Johnson & Johnson vaccine, the efficacy was 72% in the U.S., 66% in Latin America, and 57% in South Africa. Notably, 95% of the COVID-19 cases in South Africa were due to the 501Y.V2 variant.

Although the Novavax and Johnson & Johnson vaccines were less effective against the 501Y.V2 variant, many researchers are quick to point out, that even at this level of efficacy, these vaccines could still play a significant and even vital role in controlling the pandemic. "I am encouraged that they remained partially effective, about as good as seasonal flu vaccines," says David Montefiori, Professor and Director of the Laboratory for AIDS Vaccine Research and Development at Duke University Medical Center.

An obvious advantage of the Johnson & Johnson vaccine is that it is a single shot, and given the spread of these viral variants, accelerating the rollout of vaccines will be crucial. The company plans to seek an Emergency Use Authorization from the U.S. Food and Drug Administration early this month.

"It looks like we have two more vaccines in the armamentarium to battle this pandemic, each of which has its advantages in terms of efficacy, cost, logistics, and ease of administration," says Jonathan Carapetis, Director at Telethon Kids Institute and an Australian pediatric physician who specializes in infectious diseases. "The announcements from Novavax and Johnson & Johnson are overall good news, but also something of a reality check."

John Moore, Professor of microbiology and immunology at Weill Cornell Medical College, is less convinced that a single shot of Johnson & Johnson's vaccine is enough. "The potency of the Novavax vaccine is at least on par with the two mRNA vaccines and, once approved, will become very useful. Although it also requires two doses, it can be shipped and stored at four degrees Celsius, which is beneficial," he says. "I'm significantly less enthusiastic about the Johnson & Johnson vaccine, which is clearly weaker than the others. A second dose may overcome some of its limitations."

Meanwhile, Moderna announced that laboratory studies indicate that its two-shot mRNA vaccine induced six-fold lower levels of neutralizing antibodies against the B.1.351 variant. This finding prompted the company to explore strategies for enhancing immunity against B.1.351 and other emerging viral variants, even though they say the antibody levels induced by their vaccine are still likely to be protective.

Moderna will test an additional dose of its vaccine to try to boost neutralizing antibody levels in vaccinated volunteers. The company will also develop a booster candidate specifically against the B.1.351 variant. The mRNA technology that both the Moderna and Pfizer/BioNTech vaccines employ offers great flexibility, and this may prove to be an asset in the battle against COVID-19. "I believe the vaccine manufacturers will have a boost to increase protection against 501Y.V2 in the near future," says Montefiori.

Given how the COVID-19 vaccine landscape and the virus itself are evolving, scientists are also increasingly concerned about future variants that may emerge. "My greater concern, shared by many others, is that the virus will continue to evolve to escape the vaccine more completely," says Montefiori. "Scientists need to be monitoring and studying new variants in real time to provide an early warning and to facilitate next generation vaccines if necessary."

Stanley Plotkin, veteran vaccine developer, Emeritus Professor of Pediatrics at the University of Pennsylvania, and founding board chair of the Human Vaccines Project, predicts routine updates to COVID-19 vaccines may be necessary. "It certainly appears that the prospect is yearly changes to vaccines or multivalent vaccines. We need a system identical to influenza, with regional labs surveying the landscape on an ongoing basis," he says.

Carapetis agrees. "While it is important to note that both vaccines do prevent against the 501Y.V2 variant, it signals a critical need to be working now on next-generation vaccines that can be adapted to the inevitable further mutations that will be seen in SARS-CoV-2. But perhaps the most critical messages are that vaccines alone will not be a panacea—ongoing public health measures, such as those that Australia has implemented with extraordinary success, are essential—and also that we are likely to be living with this virus for many years to come."

By Kristen Jill Abboud

Spotlight on 501Y.V2 Variant

Penny Moore, Ph.D.
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Penny Moore, a Reader and researcher at the University of the Witwatersrand and the National Institute for Communicable Diseases in Johannesburg, and colleagues recently published data from laboratory experiments showing that one of the known SARS-CoV-2 variants that was first identified in South Africa (referred to as either 501Y.V2 or B.1.351) can largely, or in some cases completely, escape neutralizing antibodies developed by individuals who have recovered from COVID-19. This raised concerns about what impact, if any, this variant would have on vaccine efficacy, particularly as this variant is now present in several countries around the world.

These concerns were justified when both Novavax and Johnson & Johnson reported that their vaccine candidates were less effective overall against this viral variant than others in their Phase III clinical trials. To put all of this in perspective, HVP Editor Kristen Jill Abboud recently spoke with Moore about the 501Y.V2 variant and its implications for existing and future COVID-19 vaccines.

An edited version of the conversation appears below.

What do we currently know about the 501Y.V2 variant?

It is different from the variant that has been previously described in the U.K. It has several mutations across the full genome. It emerged in early October 2020 in South Africa and has rapidly started to dominate here. The more viral sequencing that is done, the more they are finding the new variant as it spreads across South Africa. It has nine mutations in the Spike region, which is of greatest interest from a vaccine point of view, and they are concerning parts of the Spike protein specifically because they cluster—it is always a bad sign when you see a cluster of mutations—in the receptor binding domain and in the N-terminal domain. The reason that this is concerning is because these are the immune hot spots, which are the parts of the Spike protein that are best recognized by the immune system. Just looking at that series of mutations is indicative of immune escape, and of antibody escape, specifically.

Another mutation that is of concern is the 501 mutation, which is shared with the U.K. variant, and that is concerning because it has been implicated in enhanced transmissibility.

Is the 501Y.V2 variant any more lethal?

I think that there is compelling evidence now to suggest that the 501 mutation allows the virus to bind better to its receptor and that translates into increased transmissibility. The data on whether these variants cause more severe disease is less clear at this stage. I've seen quite a lot in the press about the potential for the British variant being able to cause more severe disease, although that still seems to be undetermined. At this stage, the data for the 501Y.V2 variant does not suggest it is more likely to cause worse disease, but that is something we are looking at closely in South Africa.

What does your research show about how susceptible the 501Y.V2 variant is to antibody neutralization?

There's very strong evidence that the 501Y.V2 variant exhibits immune escape. For starters, studies by Jesse Bloom and colleagues indicate that the mutation at position 484 in this variant reduces its sensitivity to neutralization. In parallel, two studies, one from our lab and another from AHRI [Africa Health Research Institute], have both shown that the 501Y.V2 variant shows immune escape from convalescent plasma. In our case, we tested 44 samples from individuals who'd previously been infected, and we saw that in 90% of cases there was a reduction in the sensitivity of the new variant to those old antibodies, and in half of cases, a complete loss of sensitivity. That data is very well supported by the study that has come out from Alex Sigal's lab, which also shows a profound reduction in neutralization using a different assay.

Does this mean people who have already been infected with SARS-CoV-2 could be reinfected with this new variant?

It raises the possibility of increased reinfection because it suggests that whatever antibodies people had that were able to protect them against the old variant may be less effective at protecting them against the new variant. The problem is that we don't know what that threshold of protection is, and we can't tell that from lab studies. We can only really tell that from clinical trials. The recently released data from the Novavax clinical trial, however, unfortunately also show a lack of protection against 501Y.V2 in people who have been previously infected, suggesting that the lab studies are indeed correct.

What are the potential implications for vaccines?

Different vaccines work differently, and we need to test each of them, which is exactly what we're doing. Our lab, and many others across the world, are taking plasma from people who were enrolled in vaccine trials and looking at how well those antibodies elicited by vaccination are able to block the new variant from infecting cells. For example, Moderna has reported a six-fold decrease in neutralizing antibody titers against the 501Y.V2 variant, but we don't know how serious that is in terms of vaccine efficacy. The results from the Novavax and Johnson & Johnson trials, released in the last few days, do give some insights into this question.

The South African arm of the Novavax vaccine trial showed efficacy in preventing COVID-19 of 49%-60%, depending on which groups you look at, whereas in the U.K., efficacy was 89%. Similarly, in the South African arm of the Johnson & Johnson vaccine trial, 57% efficacy was shown, reduced from 72% efficacy in the U.S. Both these trials suggest that the vaccines are less effective against 501Y.V2, but, importantly, approximately 60% protection was still observed. This is still enough to make a major impact on the South African epidemic.

I'm always asked whether I would still take the vaccine, based on this slightly depressing data around neutralizing antibodies, and I say that any vaccine that was offered to me, I would take.

Can scientists predict future mutations, or how quickly the vaccines will need to be altered to keep up with the genetic mutation of the virus?

Coronaviruses don't mutate very fast, but with all of these millions of people infected across the world who are developing pretty good antibody responses to their own viruses, there's just a huge amount of community antibody pressure on the virus. Also, we regard this as an acute infection, but sometimes people don't clear the virus as quickly as most folks do. In those cases, when you have long-term infections in the context of an arms race with the immune system, it's like the perfect storm for selecting antibody-resistant variants. We can't predict what the pressures are on the virus. We know that this virus can escape from immune pressure, as the immune pressure changes and vaccines are rolled out, that pressure might change even further.

All we can do is sequence viruses as much as we can. We can only find what we're looking for, and if we're not sequencing deeply enough, there's no chance we're going to be able to identify variants. South Africa has a really concerted, multi-site, next-generation sequencing consortium, which is why they picked up the new variant. The country has the infrastructure and the systems in place to be able to understand our viral evolution and react rapidly.

Are COVID-19 vaccines now available in South Africa?

We don't currently have a vaccine in South Africa. There are many vaccines being tested here, including those from AstraZeneca, Johnson & Johnson, and Novavax, but at this stage we don't have a vaccine that is being rolled out. The government has a fantastic and very ambitious plan to roll out the vaccine in the next couple of weeks and months. I think it will be difficult to roll out the vaccine at this massive scale, however, the first batches of vaccines are arriving in South Africa any day now.

Without a vaccine rolling out at this stage in South Africa, we're relying on the non-pharmaceutical interventions, and they work just as well as against the new variant as the old variant. It's still good to wear a mask.

Interview by Kristen Jill Abboud

Must Read

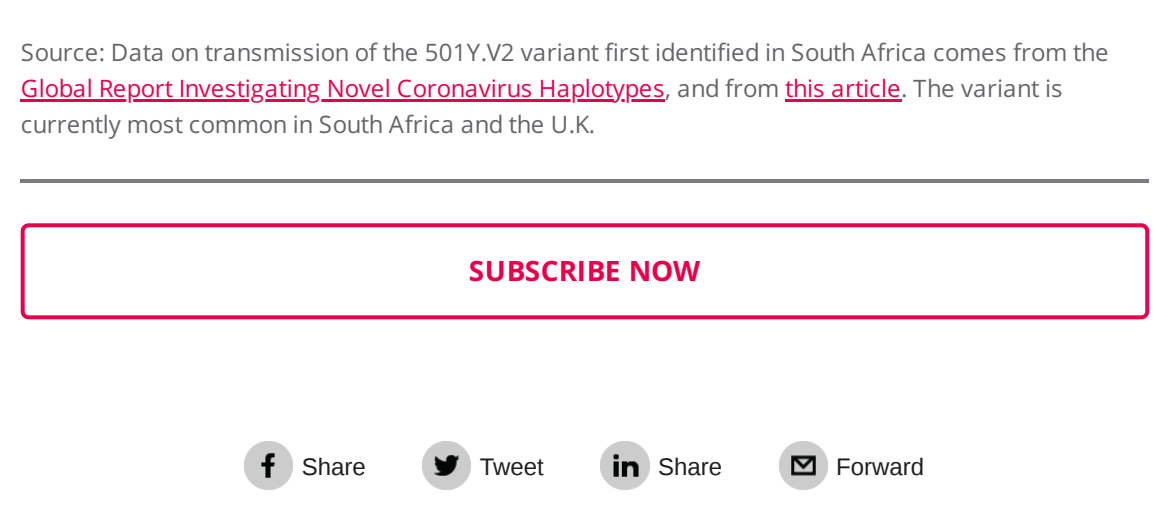
Scientists continue to study variants of SARS-CoV-2 and to evaluate whether they are susceptible to neutralization by the antibodies induced by existing COVID-19 vaccines. Other studies of note include those designed to examine the persistence of SARS-CoV-2 immunity.

- This pre-print publication shows that sera from volunteers in trials of both Pfizer/BioNTech's and Moderna's mRNA-based COVID-19 vaccines had less potent neutralizing antibodies against both the 501Y.V2 (also known as B.1.351) SARS-CoV-2 variant that was first identified in South Africa, and the 501Y.V3 variant that was first identified in Brazil.
- This pre-print publication shows that sera from individuals vaccinated with Pfizer/BioNTech's COVID-19 vaccine were able to neutralize the B.1.1.7 SARS-COV-2 variant first identified in the U.K.
- Moderna reported that its mRNA vaccine is protective against both the B.1.1.7 and B.1.351 SARS-CoV-2 variants, albeit less so against the B.1.351 variant. The company also announced it would study two strategies for boosting immunity against the emerging viral variants. Moderna plans to study adding an additional booster to its two-dose COVID-19 vaccine regimen and to test a new booster known as mRNA-1273.351 in clinical trials to specifically address the B.1.351 variant.
- This study in *Nature* showed that somatic hypermutation, enhanced potency, and maturation of antibodies occurred at more than six months following SARS-CoV-2 infection.
- In this pre-print publication, scientists assessed immunological memory to SARS-CoV-2 for up to eight months post infection in samples from 188 individuals.
- A perspective article on herd immunity to SARS-CoV-2 was recently published in *Science*. This article accompanied a study in *Science* detailing that three-quarters of the population in Manaus, Brazil were infected during the COVID-19 epidemic.
- In this study in JAMA, analytical models suggest that asymptomatic individuals are responsible for more than half of all SARS-CoV-2 transmission.
- In this pre-print publication, functional antibody and repertoire analyses were assessed in SARS-CoV-2 convalescent serum.
- This article in *JCI Insight* discusses engineered Fc variants of a cross-SARS-reactive antibody that caused increased pathology in infected mice and hamsters.

COVID-19 in Numbers

Global Transmission of the 501Y.V2 (B.1.351) SARS-CoV-2 Variant

January 28, 2021



Source: Data on transmission of the 501Y.V2 variant first identified in South Africa comes from the Global Report Investigating Novel Coronavirus Haplotypes, and from this article. The variant is currently most common in South Africa and the U.K.