Medical News & Perspectives

COVID-19 Vaccines vs Variants—Determining How Much Immunity Is Enough

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As COVID-19 cases resulting from infection with SARS-CoV-2 variants accumulate in the US and around the world, one question looms large:

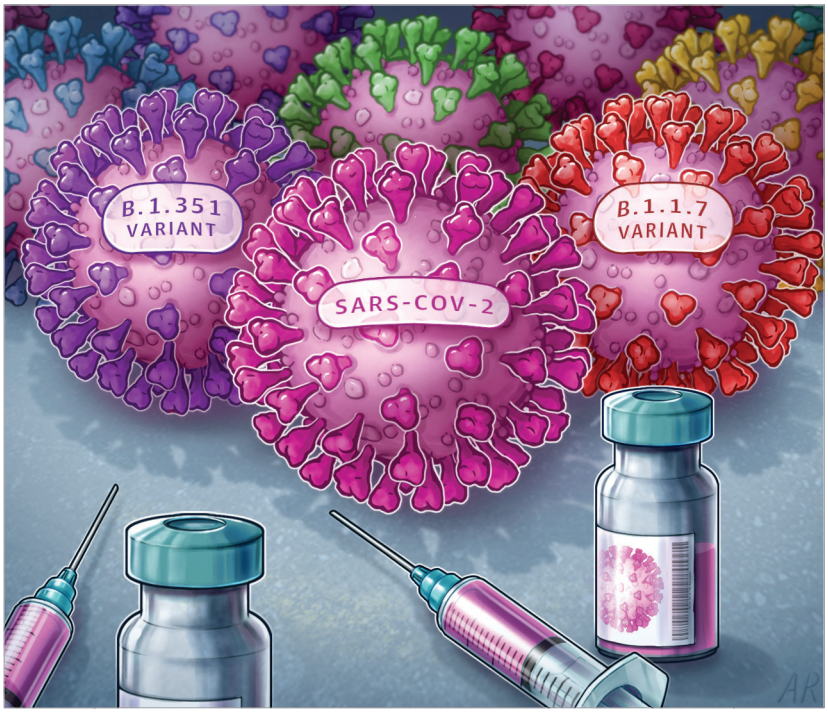
How well do the COVID-19 vaccines developed so far protect against these novel coronavirus spinoffs?

"The virus is telling us it's going to throw out a lot of mutations," infectious disease specialist Jesse Goodman, MD, MPH, who, as then-chief scientist at the US Food and Drug Administration (FDA), led the agency's response to the H1N1 influenza A pandemic, said in an interview. "Even if we don't have a critical situation right at the moment-...there's a realistic possibility that variants will continue to evolve that have potential to avoid vaccine immunity."

That's to be expected, Anthony Fauci, MD, director of the National Institute of Allergy and Infectious Diseases (NIAID), told *JAMA* Editor in Chief Howard Bauchner, MD, in a February 3 podcast. Regardless of the platform on which the vaccine is based, Fauci said, "you still have a fixed immunogen and a virus that's changing. Sooner or later, you're going to get a mutant that evades that."

One reason SARS-CoV-2 is throwing out variants and will continue to do so is because relatively few people globally have been vaccinated, Norman Baylor, PhD, a former director of the FDA's Office of Vaccines Research and Review, noted in an interview. "This virus is like, 'Yep, I've got plenty of people I can infect, and the more I replicate, the more I can mutate,'" Baylor said.

Some scientists have used the term *vaccine resistance* to describe the reduced efficacy of COVID-19 vaccines against some variants. But that confuses matters by suggesting vaccines are analogous to antibiotics, University of Washington biologist Carl Bergstrom, PhD, who studies evolution and medicine, said in an interview. "The key point for me is that in antibiotic resistance, the changes happen in people who are on antibiotics," he said, while antigenic escape by SARS-CoV-2 occurs in people who *haven't* been vaccinated.



When viruses replicate, Penn State biologist David Kennedy, PhD, explained in an interview, the cycle is like a classic childhood game. "Viruses copying themselves, it's almost like a game of telephone," said Kennedy, who studies pathogen evolution. "They repeat what they thought they heard, so they make mistakes all the time."

Despite those many mistakes, Kennedy noted, he's unaware of any vaccines against viral diseases other than seasonal flu that have had to be updated because of changes in the virus. Hepatitis B virus developed "vaccine escape mutations," but they posed no health risks, he said.

Good Enough?

Current COVID-19 vaccines are based on the SARS-CoV-2 spike protein, which the virus uses to bind to and infect host cells, of the original Wuhan-hu-1. But the emerging "variants of concern"—deemed so because they appear to be more transmissible or deadlier than the wild-type SARS-CoV-2—contain mutations in the spike protein, spurring vaccine efficacy concerns.

Trials of the Novavax, Janssen/Johnson & Johnson, and AstraZeneca vaccines in South Africa, where the B.1.351 variant of concern represents virtually all of the circulating SARS-CoV-2, seemed to justify those concerns. The South Africa trials found lower vaccine efficacy compared with trials in other countries where B.1.351 wasn't dominant.

The pivotal trials of the Pfizer-BioNTech and Moderna vaccines, the first 2 authorized by the FDA, were conducted mainly in the US before any cases of infection by B.1.351 or other variants of concern had been detected in the country.

Much of the current data on the messenger RNA (mRNA) vaccines' efficacy against SARS-CoV-2 variants has come from laboratory studies in which researchers exposed serum samples from immunized individuals to genetically engineered versions of concerning variants and then measured neutralizing antibody titers. Such

studies repeatedly have shown the vaccines elicit lower levels of neutralizing antibodies against SARS-CoV-2 variants than against older, more common isolates.

For example, in a February 17 letter to the editor in *The New England Journal of Medicine*, scientists described testing serum samples from individuals immunized with 2 doses of the Pfizer-BioNTech vaccine against recombinant viruses containing some or all of the spike protein mutations found in the B.1.351 variant. Neutralization of B.1.351 was approximately two-thirds lower than that of USA-WA1/2020, an early SARS-CoV-2 isolate.

In another letter published the same day, researchers reported measuring neutralizing antibody activity in serum samples from participants in the phase 1 trial of the Moderna COVID-19 vaccine. One week after the participants received the second dose, neutralizing antibody titers induced by a recombinant virus bearing the B.1.351 spike protein were 6-fold lower than those induced by a recombinant virus bearing the original Wuhan-Hu-1 spike protein.

However, that still might be sufficient to protect against COVID-19, or at least severe COVID-19.

"Fortunately, neutralization titers induced by vaccination are high, and even with a 6-fold decrease, serum can still effectively neutralize the virus," Fauci and 2 NIAID colleagues wrote in a *JAMA* editorial posted February 11. And, they noted, lower vaccine efficacy in the South African clinical trials could be related to geographic or population differences.

Although serum antibody levels correlate well with protection for many infectious diseases, protective levels haven't yet been determined for SARS-CoV-2. They may never be established, Baylor said. "With some organisms, it's very difficult to pinpoint exactly what level of [antibody] response is needed," he said, citing the bacterium that causes pertussis as one such microbe.

In addition to neutralizing antibodies, mRNA vaccines also induce virus-specific helper T cells and cytotoxic T cells that might help protect against infection, Paul Offit, MD, director of the Children's Hospital of Philadelphia's Vaccine Education Center, and John Moore, PhD, a microbiologist and immunologist at Weill Medical College of Cornell University, noted in a *JAMA* viewpoint published recently.

Assays of serum samples from participants in the phase 1 and phase 3 trials of Johnson & Johnson's adenovirus-based vaccine, which the FDA authorized for emergency use on February 27, suggest that neutralization correlates with protection but probably is not the only biomarker that does, Johan Van Hoof, MD, who oversees vaccine research and development at Janssen, a Johnson & Johnson subsidiary, said February 26 during an FDA advisory committee meeting.

Experiments vs Experience

Without immune correlates of protection, only real-world experience can provide answers about COVID-19 vaccines' efficacy against illness and death from SARS-CoV-2 variants.

"For right now, you know that a line is crossed if you see people fully immunized with the vaccines [who], nonetheless, when infected with the variants, are being hospitalized," Offit said at a February 4 COVID-19 Vaccine Analysis Team press briefing.

At first glance, findings from a phase 2 trial of the Oxford-AstraZeneca vaccine in South Africa seemed quite discouraging, spurring that country to suspend its planned rollout of the vaccine. The trial found that the vaccine did not protect against mild to moderate COVID-19 caused by the B.1.351 variant. The findings, posted February 12, had not been peer reviewed.

However, "the study was not really designed to determine whether the vaccine could protect against severe COVID or not," principal investigator Shabir Madhi, MBBCH, PhD, a vaccinologist at the University of the Witwatersrand, Johannesburg, and cofounder and codirector of the African Leadership Initiative for Vaccinology Expertise, said in a February 7 briefing about the results. Participants, who numbered only about 2000, were young—average age 31 years—and healthy, so their risk of severe disease was low, vaccinated or not, explained Madhi, who also led Novavax's vaccine trial in South Africa.

Novavax and Janssen conducted larger trials in South Africa than Oxford and AstraZeneca. Although both of their vaccines had lower efficacy rates in South Africa than in trials in other countries, vaccinated participants who received the Janssen vaccine were still less likely to require hospitalization for COVID-19 than those who received placebo shots, and Madhi recently told Nature he expected that to be the case with the Novavax vaccine as well.

Goodman concurred. "It's consistent with how the immune system works," he said, explaining that although protection against B.1.351 might be incomplete, vaccines could still protect against severe COVID-19. In regard to the Oxford-AstraZeneca vaccine, he said, "my guess is it will be like the other vaccines and have some effect" against B.1.351.

As Baylor, a consultant on vaccines for the World Health Organization, noted, "One of the biggest things you want to do in a pandemic is keep people from dying and keep them out of the hospital."

That appears to be happening.

COVID-19 cases and hospitalizations started to decline in mid-January in Israel, which leads the world in percentage of the population vaccinated. Larger and earlier decreases occurred among older individuals, who were a top priority for vaccination, according to an article posted February 9 that had not been peer reviewed. In the week before the study was posted, COVID-19–related hospitalizations declined by 36% and 29% fewer patients were severely ill with COVID-19 than 3 weeks earlier. The B.1.1.7 variant, first identified in the UK, is now the dominant SARS-CoV-2 variant in Israel as well as in the UK. That variant doesn't appear to reduce neutralizing antibodies to the same extent as B.1.351.

Similarly encouraging UK data, although not peer reviewed, were posted in February.

In Scotland, researchers estimated that Pfizer-BioNTech's vaccine was up to 85% effective and Oxford-AstraZeneca's vaccine up to 94% effective in preventing COVID-19–related hospitalizations 28 to 34 days after a single dose—the UK policy is to provide the second dose 12 weeks later.

A Public Health England (PHE) report on immunization with the Oxford-AstraZeneca or Pfizer-BioNTech vaccine noted that "early data suggest that any cases that do occur in older vaccinated people are around half as likely to lead to hospitalisation and/or death." The data came from those vaccinated only 14 days earlier; lower rates of hospitalization and death would likely be seen in people vaccinated more than 3 or 4 weeks earlier, the report noted.

Stopping the Spread

The US Centers for Disease Control and Prevention advises that even after they're fully vaccinated, people should continue to mask

up and socially distance in public places in part because they could still unknowingly become infected and, although asymptomatic, transmit SARS-CoV-2 to people who haven't yet received their shots.

Transmission by infected asymptomatic vaccinees could provide an opportunity for more virulent variants to spread, Kennedy suggested in a 2015 article. The article described an experiment with a herpes virus that causes Marek disease in chickens. Vaccines against Marek disease are described as "leaky" because, although they protect chickens from getting sick, they don't prevent them from becoming infected and transmitting the virus to unvaccinated chickens. That allows the most virulent strains that normally would die along with an infected chicken to survive and infect and kill unvaccinated chickens, the experiment found.

Fortunately, as the article notes, nearly all vaccines used in humans prevent asymptomatic infection and spread.

"In general, vaccines that are effective in reducing infections do have major impacts on reducing transmission," said Goodman, director of Georgetown University's Center on Medical Product Access, Safety and Stewardship. "It is probable that these vaccines will reduce transmission."

Mounting evidence supports that notion. In a study of UK health care workers immunized with the Pfizer-BioNTech vaccine, participants underwent biweekly polymerase chain reaction testing and twice weekly rapid antigen testing to help investigators determine rates of asymptomatic and symptomatic infections.

The study, posted February 22 but not peer reviewed, found a 70% reduction in both types of infection 21 days after participants received their first dose and an 85% reduction a week after receiving their second dose. "Overall, we're seeing a really strong effect to reducing any infection—asymptomatic and symptomatic," coauthor Susan Hopkins, MD, PHE strategic response director, said at a press conference. In March, Pfizer and BioNTech announced that non–peer-reviewed data from Israel showed their vaccine was 94% effective against asymptomatic SARS-CoV-2 infection.

Next Steps

Whether COVID-19 will join influenza as an infectious disease for which annual vaccination is required isn't yet known. Although they're both RNA viruses, "the backdrop is so different," Baylor said. "We are in a pandemic. We didn't have a vaccine. This [mRNA vaccines] is new technology."

Short of developing a universal vaccine that protects against most SARS-CoV-2 variants, "we need to be prepared to make alterations in the existing [COVID-19] vaccines to deal with [variants] that emerge," Goodman said.

Out of what they call an abundance of caution, manufacturers say they're developing strategies to deal with the possibility of a variant that escapes coverage by first-generation vaccines.

At the February 26 FDA advisory committee meeting, Van Hoof said Janssen plans to launch a phase 1 trial of a SARS-CoV-2 variants vaccine by this summer.

Pfizer and BioNTech announced February 25 that they had begun evaluating the safety and immunogenicity of a third dose of their vaccine to see whether it would boost immunity to SARS-CoV-2 variants. In addition, the companies said they are discussing with regulatory agencies, including the FDA, a clinical study to evaluate a modified vaccine based on the B.1.351 variant. "The companies are hoping to pursue the validation of future modified mRNA vaccines with a regulatory pathway similar to what is currently in place for flu vaccines," according to a press release.

Moderna announced February 24 that it had shipped a booster vaccine candidate based on B.1.351 to the NIAID for a phase 1 trial. And Novavax, whose first-generation vaccine hasn't been authorized yet in the US, announced January 28 it was working on developing a booster, a combination bivalent vaccine, or both to protect against variants. The company said it expected to begin clinical trials in the second quarter of 2021.

Modifying vaccines to target variants isn't difficult. For example, with Pfizer-BioNTech's and Moderna's mRNA vaccines, "it's very convenient, because, basically, all you do is change a computer program and the synthetic for the synthesizing portion of this and you can change the vaccine," Peter Marks, MD, PhD, director of the FDA's Center for Biologics Evaluation and Research, which regulates vaccines, said during a January 29 American Medical Association (AMA) webinar. "But the question is, what do we need from the FDA perspective to feel comfortable having that deployed."

On February 22, the FDA updated its nonbinding guidance for vaccine manufacturers to include information about what the agency would like to see when evaluating vaccines that have been modified to address emerging SARS-CoV-2 variants.

The updated guidance advises manufacturers to conduct studies comparing neutralizing antibody responses to SARS-CoV-2 induced by the modified vaccine with those induced by the prototype vaccine. One such study should use serum samples from people who hadn't been previously vaccinated or infected with SARS-CoV-2, while another study would use serum samples from people previously vaccinated with a prototype vaccine who then received an experimental booster against variants of concern.

The Hard Part

Modifying COVID-19 vaccines would probably be the most straightforward step in dealing with SARS-CoV-2 variants. "For vaccines and biologics, it's the manufacturing process that defines the product, and the manufacturing process isn't changing," Baylor explained.

More challenging will be deciding when and how to deploy COVID-19 vaccines 2.0. The influenza model, in which surveillance during the Southern Hemisphere's flu season identifies the circulating strains to target with vaccines in the Northern Hemisphere's coming flu season, doesn't work for SARS-CoV-2, Baylor noted.

"The challenge for COVID is what variant do you pick" when modifying a vaccine, he said. "How often does it change?"

Once that's decided, would people who've already received the original COVID-19 vaccine get a booster shot to protect against variants of concern while vaccine-naive individuals receive the original vaccine and the booster rolled into one? "Do we have the capacity to make both?" Baylor asked.

Plus, the need to deploy vaccines or boosters targeting new variants would complicate the already rocky rollout of COVID-19 vaccines, in part due to inexperience in vaccinating US adults en masse.

"How do we deploy this?" Baylor said of next-generation COVID-19 vaccines. "When do we pull the trigger to actually do this?" ■

Note: Source references are available through embedded hyperlinks in the article text online.