Medical News & Perspectives

Questions Remain About What SARS-CoV-2 Variants Should Go Into the Annual COVID-19 Vaccines Proposed by the FDA

Rita Rubin, MA

From the beginning, a scorecard might have come in handy for keeping track of the whos, whats, and whens of COVID-19 vaccination.

Both available messenger RNA (mRNA) vaccines and the Novavax protein subunit vaccine require a 2-dose primary series, but the interval between the 2 shots is a minimum of 3 weeks or 4 weeks, depending on the manufacturer. And the primary series for Johnson & Johnson's viral vector vaccine, now only in limited use, is a single dose.

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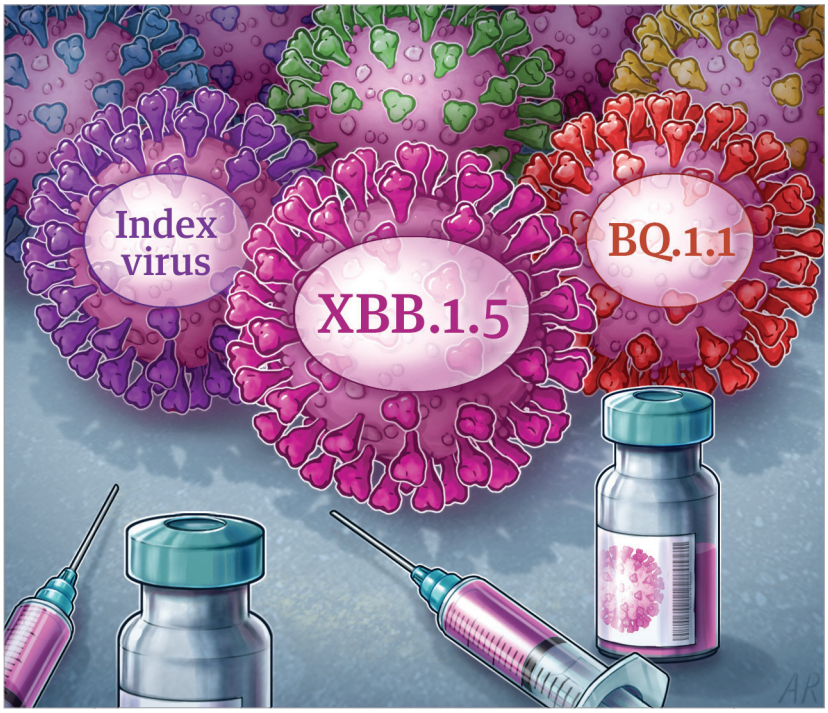
When protection against mild to moderate COVID-19 from primary vaccines began to wane, recommendations came out about getting another dose, depending mainly on age and immune competency. Then, in an effort to protect against increasingly immune-evasive Omicron variants, bivalent mRNA vaccine boosters replaced monovalent boosters last September, but monovalent vaccines are still being administered to people who haven't yet received their primary series.

Three years into the COVID-19 pandemic and more than 2 years since vaccines became available, however, the US Food and Drug Administration (FDA) wants to get down to 1 vaccine dose per year for most people, following an annual review of the circulating SARS-CoV-2 variants du jour to determine the shot's optimal makeup. Under the FDA's proposed plan, everyone's annual vaccine, administered in the fall, would be composed of the same variant or variants, no matter whether it's their 1st or 5th or 15th dose. ("I think this virus is going to be with us forever," vaccine expert Paul Offit, MD, said in an interview.)

At the most recent meeting of the FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC) in late January, the 21 voting members unanimously decided in favor of "harmonizing the vaccine strain composition of primary series and booster doses in the US to a single composition," the only question on which the agency asked them to vote.



This is essentially the same approach taken with seasonal influenza vaccines, a strategy FDA scientists think will simplify COVID-19 vaccine administration and increase uptake, which has been abysmal for the bivalent boosters.

However, as several FDA scientists and outside advisors noted at the meeting, SARS-CoV-2 is not the flu. "I'm the first one to say you can take some lessons from [influenza], but…they are different viruses," Jerry Weir, PhD, director of the Division of Viral Products at the FDA's Center for Biologics Evaluation and Research (CBER), told committee members.

Both SARS-CoV-2 and influenza viruses can cause great numbers of potentially fatal respiratory infections, although vaccines for each protect against serious illness. But no one is yet calling SARS-CoV-2 infection "seasonal COVID-19," so the optimal timing of annual COVID-19 vaccinations remains somewhat uncertain.

And while influenza viruses typically sweep across the world, boosting confidence in strain selection for the annual vaccine, that hasn't necessarily been the case with SARS-CoV-2 variants. After all, who in the US remembers Mu, a variant of concern first identified in Colombia that didn't spread much beyond Central and South America?

Monovalent, Bivalent, More?

The FDA plans to reconvene VRBPAC in May to hash out which SARS-CoV-2 variants should be included in vaccines this fall, CBER Director Peter Marks, MD, PhD, told committee members at the January meeting.

One question is whether to keep the spike protein of ancestral SARS-CoV-2, or the index virus, which hasn't been detected in nearly 3 years, in the vaccine.

The decision last year to keep the index virus as part of a bivalent vaccine was the best one based on the evidence at the time, Kanta Subbarao, MBBS, MPH, chair of the World Health Organization's (WHO's)

Technical Advisory Group on COVID-19 Vaccine Composition, said in an interview.

Much was known about the behavior of the index virus–based vaccines, including that they offered very good protection against variants, she explained. "We were reluctant to abandon the benefits we had" from those vaccines, she said.

Combining a component of the index virus with a component of the antigenically distinct Omicron variant "was a way of hedging our bets," said Subbarao, director of the WHO's Collaborating Centre for Reference and Research on Influenza in Melbourne.

But today, "I think things have moved along very significantly from that point," she said. "We're in a very different place. There are a lot more data on Omicron infection and vaccination."

A clinical trial sponsored by the National Institute of Allergy and Infectious Diseases (NIAID) is comparing the safety and immunogenicity of prototype and variant boosters, either alone or combined, in previously vaccinated volunteers with or without a prior SARS-CoV-2 infection.

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>
> **John Beigel, MD**

All the vaccines were safe and well-tolerated, according to preliminary results from the COVID-19 Variant Immunologic Landscape (COVAIL) trial posted last July but not yet peer-reviewed. As far as immunogenicity, "any booster, including prototype, improves antibody titers across all strains," COVAIL investigator John Beigel, MD, told VRBPAC members at the January meeting. "Yes, they all work, but anything besides prototype does it slightly better."

In other words, "changing the components increases the antibody titers…toward the newer variants," Beigel, associate director for clinical research in the NIAID's Division of Microbiology and Infectious Diseases, said in an interview.

COVAIL participants with a prior SARS-CoV-2 infection had higher antibody titers after boosting than those who didn't have a prior infection, although it isn't clear how long that lasts, Beigel noted. "Getting COVID does indeed change your immune response to subsequent vaccines," he said.

Why not include all the major circulating Omicron subvariants in the COVID-19 vaccine? That's not unheard of: every flu vaccine is now quadrivalent, which means they each include 4 different influenza strains.

But this is another example of how SARS-CoV-2 is not influenza.

"From the manufacturing side, it increases complexity and, therefore, increases cost," Beigel said of adding components of multiple subvariants to vaccines. And from the science side, he explained, "it doesn't necessarily broaden the immune response much better" because, unlike the various influenza strains, the Omicron subvariants are relatively close to each other on the antigenic map.

As a VRBPAC member, Offit voted to recommend using the same vaccine composition for both the primary series and boosters. But he diverges from the FDA and some of his fellow VRBPAC members on what the composition should be and how frequently it should be administered.

Two weeks before the committee's most recent meeting, Offit, a professor of vaccinology and of pediatrics at the University of Pennsylvania's Perelman School of Medicine and director of the Vaccine Education Center at Children's Hospital of Philadelphia, published "A Cautionary Tale" about bivalent COVID-19 vaccines.

In his opinion piece, Offit, coinventor of the rotavirus vaccine, noted that data presented by Pfizer-BioNTech and Moderna about their bivalent boosters in 2022 was "underwhelming." Those boosters, which consisted of mRNA directed against the index virus and BA.1, the original Omicron variant, resulted in neutralizing antibody levels that were 1.5 to 1.75 times as high as the monovalent boosters targeting only the ancestral virus—a difference unlikely to be clinically significant, Offit wrote.

He also cited 2 studies published alongside his article that found that monovalent and bivalent boosters resulted in comparable levels of neutralizing antibodies against SARS-CoV-2 variants. One study found "no significant difference in neutralization of any SARS-CoV-2 variant," including BA.4 and BA.5, between the monovalent and bivalent boosters. The other study found comparable neutralizing antibody titers as well as T-cell responses, which weren't substantially augmented, following both monovalent and bivalent boosters.

Offit attributes these findings to immune imprinting. The monovalent primary and booster vaccines primed the immune system to the ancestral SARS-CoV-2 strain, he explained. Therefore, the immune system probably responded to the epitopes—the portion of an antigen that stimulates an immune response—that BA.4 and BA.5 share with the index virus but not to the epitopes unique to the Omicron variants.

"I do think it's important to get closer to the circulating strains for certain groups," specifically, the very old, such as his 94-year-old mother, and other high-risk groups that don't mount a strong immune response to vaccines, Offit said at the January VRBPAC meeting. But boosting healthy young people every year with vaccines targeting new SARS-CoV-2 variants is unnecessary, he said.

The Matter of Timing

For the seasonal influenza vaccines, the VRBPAC meets in February or March each year to hear presentations about what flu viruses are circulating and make recommendations about the composition of US vaccines for the fall. This gives manufacturers about a 6-month lead time to update and produce the tens of millions of doses that will be needed. More often than not, the strains selected for the vaccine early in the year are an adequate match to influenza viruses circulating in the fall and winter.

But in 2022, VRBPAC didn't meet until June 28 to consider whether COVID-19 vaccine boosters should be updated with an Omicron component. Less than 48 hours after the panel voted 19 to 2 (Offit was one of the dissenters) in favor of doing so, the FDA announced that manufacturers should add the spike protein for Omicron variants BA.4 and BA.5 to the prototype vaccine for booster vaccines in the fall.

When the FDA announced that decision, BA.4 and BA.5, whose spike proteins are identical, represented 35% of circulating SARS-CoV-2, and BA.5 became increasingly

dominant over the summer. But then even more immune-evasive Omicron subvariants, namely XBB.1.5, BQ.1, and BQ.1.1, began to take over. By the week ending February 4, XBB.1.5 represented an estimated two-thirds of circulating variants in the US, with BQ.1.1 and BQ.1 representing nearly all of the rest, according to the COVID Data Tracker maintained by the US Centers for Disease Control and Prevention (CDC). Meanwhile, BA.4 was nowhere to be found, and BA.5 represented a measly 0.5% of circulating variants.

"The objective, of course, is not to chase variants" when deciding the composition of an updated COVID-19 vaccine, the FDA's Weir told VRBPAC members. "None of us think that's realistic."

And so far, it doesn't appear to be necessary to prevent serious illness and death from the virus. Although the US population has been vaccinated and boosted with vaccines directed at SARS-CoV-2 variants and subvariants that no longer appear to be circulating, the number of COVID-19 deaths per 100 000 people has remained near all-time lows through the fall and winter, the COVID Data Tracker shows.

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The mRNA platform allowed manufacturers to create and manufacture their bivalent vaccines with only about 2 months' notice, which led Weir to say that meeting in late May or early June to decide the composition of the COVID-19 vaccine "seems reasonable and practical." But Novavax, which doesn't yet make a bivalent vaccine, may need the same 6-month lead time that flu vaccine companies get, Filip Dubovsky, MD, the company's executive vice president and chief medical officer, told VRBPAC members.

A fall COVID-19 vaccination campaign may make sense for countries with temperate climates, such as the US, Subbarao said, even though not enough is known about the seasonality of the virus. People stay indoors more when temperatures drop, increasing the chance of respiratory virus transmission, she noted.

"There are good reasons to want to do a fall-winter [vaccination] campaign in climates that have a cold winter," she said. "Whether that's true for nontemperate climates is not clear." For example, influenza circulates year-round in tropical climates and peaks during the rainy season.

Upping the Uptake

One rationale for adapting the seasonal influenza vaccine model is the hope that simplifying the SARS-CoV-2 vaccine schedule will spur more people to get vaccinated.

"Having vaccines is not sufficient," VRBPAC member Archana Chatterjee, MD, PhD, dean of the Chicago Medical School at Rosalind Franklin University, noted at the January meeting. "We need to have them used."

As of February 9, only 15.7% of eligible US residents had received the bivalent COVID-19 vaccine, which had been available for 5 months, according to the COVID-19 tracker.

"I don't think there's a good argument that [annual COVID-19 vaccines] would improve uptake in older children and adults," James Campbell, MD, a pediatrics professor who has led COVID-19 vaccine trials at the University of Maryland School of Medicine, told *JAMA*.

Until she asked them, Alyssa Sinclair, MA, assumed that the main reason people weren't getting the bivalent booster was because of safety concerns stemming from misinformation. After surveying 1200 people in November and early December, she found that she'd been mistaken. Instead, the most common reasons cited for not getting the bivalent booster were lack of awareness of eligibility or availability and overconfidence in existing immunity, Sinclair and her coauthors recently reported in *Morbidity and Mortality Weekly Report (MMWR)*.

"Switching to an annual scheduling could help simplify the messaging," Sinclair said in an interview.

But that move alone is unlikely to spur many people to get an updated vaccine.

"I think we need other strategies to improve uptake," Sinclair said. "People think they're already protected enough. People aren't aware of waning immunity. If they think they don't stand to benefit, why would they go through the hassle to get it?"

Switching to an annual schedule where people get a vaccine for COVID-19 and a seasonal influenza vaccine at the same time wouldn't immediately increase COVID-19 vaccine uptake, she said, noting that the demand for annual influenza vaccination isn't as brisk as it could be. (Overall, 49.4% of US adults aged 18 years or older received an influenza vaccine during the 2021-2022 flu season, according to the CDC; coverage was lowest among American Indian/Alaska Native, Black, and Hispanic people.)

"But I think there's an opportunity here if the messaging is done well," said Sinclair, who will graduate from Duke University in the spring with a PhD in psychology and neuroscience. Something along the lines of "we've updated this formula to help protect you against what's out there now," would probably work, she said.

What's the Point?

Expectations for COVID-19 immunization range from preventing transmission and asymptomatic infection—which is likely impossible with current vaccines—to keeping infected people out of the hospital.

Elimination of the virus before it replicates in the host, known as sterilizing immunity, is going to be difficult to achieve with COVID-19 vaccines because of SARS-CoV-2's short incubation period, noted Campbell, an infectious disease specialist at the University of Maryland Children's Hospital. The incubation period doesn't provide enough time for immunological memory to kick in and routinely prevent people from getting sick and transmitting the virus.

"You're not going to get protection against mild illness for any length of time," Offit said. "My goal for myself, for the country, is to get people used to the idea that they might get a mild infection."

He can pinpoint when he realized that vaccinating to protect against severe COVID-19 illness was enough: July 2021, when 469 cases of SARS-CoV-2 Delta infection associated with multiple large public gatherings were identified in Provincetown, Massachusetts. Three-quarters of those infected had been vaccinated, according to a report in *MMWR*.

Only 5 of the infected people were hospitalized. Four of them were vaccinated, and no one died. To Offit, the glass was half full, not half empty. "It's a win," he said.

Subbarao and Beigel, on the other hand, would disagree that the end goal of COVID-19 vaccination is prevention only of serious illness, hospitalization, and death.

"Ideally, we do want a vaccine that will prevent transmission," Subbarao said.

Current data show that the available COVID-19 vaccines do decrease transmission and asymptomatic infection to an extent, Beigel noted. For example, a fifth of the vaccinated people who became infected in the Provincetown 2021 outbreak had no symptoms.

"The more we can minimize any of these outcomes, the better," he said. "There are still people being hospitalized."

However, further reducing transmission and asymptomatic and mild infection "is probably beyond giving more of just the same vaccine," Beigel said. "Realistically, you need to think about mucosal vaccine."

Such vaccines would be squirted or sprayed into the nose, where SARS-CoV-2 enters the body. Theoretically, they would block the virus from replicating there, preventing symptoms and transmission via coughing or sneezing. And it's likely they'd be more acceptable than injections for many people, Campbell pointed out.

As Subbarao said, "there's a lot that we have yet to learn about this virus, and there's a lot we've learned in the past year." ■

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Conflict of Interest Disclosures: Dr Campbell reported being the principal investigator for vaccine studies for which his university has received payments from Emergent Biosciences, FluGen, GSK, Merck, Moderna, Novavax, and Pfizer. No other disclosures were reported.

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