Medical News & Perspectives

COVID-19 Boosters This Fall to Include Omicron Antigen, but Questions Remain About Its Value

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Probably many people who watched or participated in the June 28 virtual US Food and Drug Administration (FDA) advisory committee meeting about updating COVID-19 vaccines could agree on 1 point, made by the agency's Peter Marks, MD, PhD:

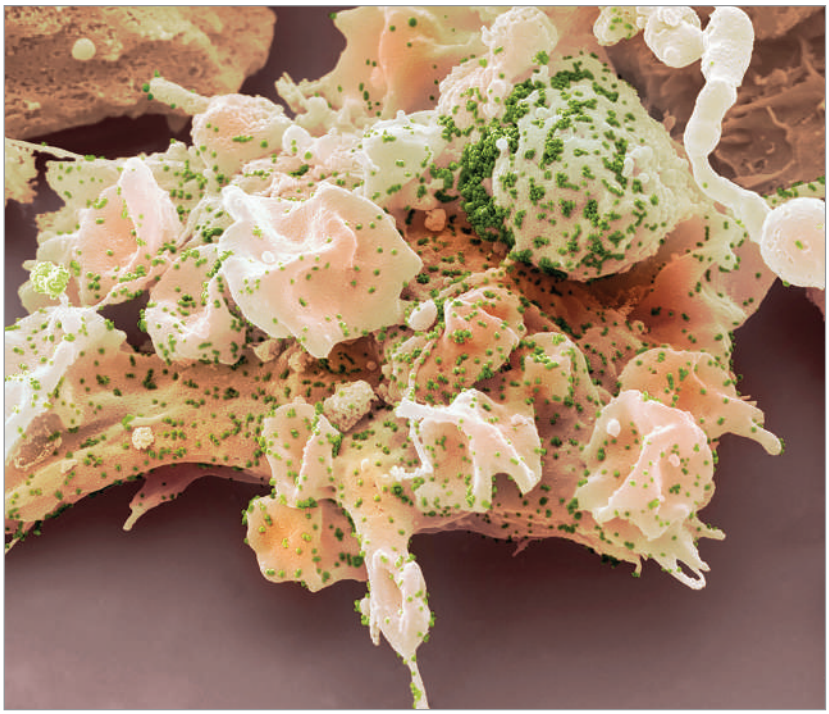
"It is science at its hardest."

The FDA convened its Vaccines and Related Biological Products Advisory Committee (VRBPAC) to discuss whether to add an Omicron component to boosters for the fall. In order to have enough doses by early October, "we will need to very rapidly move to let companies know what that selection will be," Marks reminded the panelists. (How many doses will be enough isn't clear—as of June 30, only 51.1% of fully vaccinated US adults aged 18 years or older had received 1 booster shot, while only 27% of fully vaccinated adults aged 50 years or older, for whom a second booster is recommended, had received 2, according to government data.)

Medical News website

Omicron, which the World Health Organization (WHO) classified as a variant of concern (VOC) in November 2021, is the first VOC that can evade the immune system, resulting in lower vaccine effectiveness, the WHO's Kanta Subbarao, MBBS, MPH, told committee members. Even so, she noted, after a booster dose, the available prototype vaccines, which are based on the ancestral SARS-CoV-2 index virus strain that has long been undetectable among circulating viruses, continue to protect people against serious illness and death.

After a day of listening to presentations by Subbarao, director of the WHO's Collaborating Centre for Reference and Research on Influenza in Melbourne, and scientists from the FDA, the Centers for Disease Control and Prevention (CDC), and 3 vaccine manufacturers—Moderna, Pfizer, and Novavax—the advisory committee voted 19-2 to recommend inclusion of a SARS-CoV-2 Omicron component for COVID-19 booster vaccines this fall.



The SARS-CoV-2 Omicron variant is shown as green dots budding from a vero mammalian kidney epithelial cell 36 hours after infection.

Steve Gschmeissner/sciencesource.com

Less than 48 hours later, the FDA, which usually follows advisory committee recommendations after such lopsided votes, announced that manufacturers seeking to update COVID-19 vaccines should add a spike protein component of the Omicron subvariants BA.4 and BA.5 (which differ only outside the spike protein) to their prototype vaccines to make bivalent boosters that can be used beginning this fall. "[W]e have not advised manufacturers to change the vaccine for primary vaccination, since a primary series with the FDA-authorized and approved COVID-19 vaccines provide a base of protection against serious outcomes of COVID-19 caused by circulating strains of SARS-CoV-2," Marks, director of the agency's Center for Biologics Evaluation and Research, said in the announcement.

Yet the data presented at the VRBPAC meeting were about experimental bivalent boosters that combined prototype vaccines with the spike protein of the original Omicron variant, BA.1. When the advisory committee reconvened after lunch, Marks noted that in the week ending June 25, BA.4 and BA.5 represented more than half of US circulating SARS-CoV-2 variants for the first time, according to newly released CDC data. By the week ending July 2, BA.5 alone represented 53.6% of US circulating SARS-CoV-2 variants, while BA.4 represented 16.5%, according to the CDC. CDC data show that BA.1, which represented about a third of circulating US variants on March 26, was undetectable by May 21—an illustration of just how quickly SARS-CoV-2 is evolving.

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"No Compelling Evidence"

A BA.4-BA.5 bivalent vaccine might not trigger the same immune response as the BA.1 bivalent vaccines, Paul Offit, MD, 1 of the 2 VRBPAC members who voted against recommending an Omicron booster, told *JAMA*.

"It is not reasonable to assume that data generated for an Omicron BA.1 vaccine can easily be extrapolated to BA.4 and BA.5," noted Offit, coinventor of the rotavirus vaccine and chair of vaccinology at the University of Pennsylvania's Perelman School of Medicine. "These new Omicron subvariants are highly transmissible. Therefore, they will require a very high level of neutralizing antibodies present at the time of exposure to prevent symptomatic infection."

Data presented at the VRBPAC meeting showed that, compared with a fourth dose of the prototype COVID-19 vaccine, a fourth dose of a bivalent vaccine containing a BA.1 component showed only a modest increase in neutralizing antibodies, Offit noted. "Why would we think using BA.4 or BA.5 would be any different?" he said.

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Plus, Offit noted, although the difference in antibody titers between the prototype and bivalent boosters might have been statistically significant, it wasn't necessarily clinically significant. Perhaps both boosters generate antibody titers above the as-yet undetermined threshold correlated with protection.

Before changing COVID-19 boosters' composition, Offit said, "the benefits have to be clear." For example, he said, he would have liked the vaccine manufacturers to present data about the immunogenicity for BA.4 and BA.5 after a fourth dose of their prototype vaccines compared with after a fourth dose of their experimental bivalent BA.1 vaccines. Instead, the companies presented data comparing the prototype and experimental bivalent vaccines against BA.1, which was no longer circulating in the US by late May. (Both Moderna and Pfizer representatives did note at the meeting that their BA.1 bivalent vaccines generated higher neutralizing antibody titers against BA.1 than against BA.4 and BA.5.)

"I still believe that the current vaccines are incredibly protective against severe disease," Henry Bernstein, DO, MHCM, who cast the other vote against recommending the addition of an Omicron component to this fall's boosters, said in an interview. "There was no compelling evidence that adding that new element to the vaccine was going to increase vaccine effectiveness."

One problem, said Bernstein, a professor of pediatrics at the Zucker School of Medicine at Hofstra/Northwell Health and Cohen Children's Medical Center, is that public health messaging has been confusing, giving rise to the unrealistic expectation that COVID-19 vaccines are supposed to prevent all SARS-CoV-2 infection. Bernstein previously was a member of the CDC's Advisory Committee on Immunization Practices (ACIP) and still serves as a consultant to its COVID-19 work group.

"There was no there there to vote on," Peter Hotez, MD, PhD, who is not a VRBPAC member, said in an interview of the data presented about bivalent Omicron vaccines. "I might have also voted against it, but for a different issue: My objection is there's just a lot of muddled thinking about what's coming up in the fall."

By fall, it's likely that Omicron will be in the rearview mirror, said Hotez, dean of the National School of Tropical Medicine at Baylor College of Medicine and codirector of the Texas Children's Hospital Center for Vaccine Development. "From my point [of view], there's no advantage to giving an Omicron booster." As Subbarao noted at the VRBPAC meeting, though, "we're not trying to match what may circulate. We're trying to increase the breadth of the immune response." After all, Offit noted, the prototype vaccines, which contain components of only the index SARS-CoV-2 strain, have effectively protected against severe disease caused by every variant so far.

The only justification for including Omicron components in a COVID-19 vaccine would be as part of an effort to make a universal vaccine that would protect against whatever SARS-CoV-2 variant pops up, said Hotez, who has urged White House COVID-19 Response Coordinator Ashish Jha, MD, MPH, to make a universal vaccine a top priority.

"We need an overarching coronavirus vaccination strategy for the country," Hotez said. "What we're doing is we're allowing the pharma companies to push their own agenda."

Hotez's laboratory developed the technology, which is owned by Baylor, for Corbevax, a low-cost protein subunit COVID-19 vaccine that is patent-free and being used in low- and middle-income countries in South Asia and Africa. Hotez said his laboratory is conducting preclinical research into combining Corbevax with components of SARS-CoV-1 and the SARS-CoV-2 Omicron BA.4 and BA.5 variants, which, he speculates, might generate broad enough immunity to serve as a universal vaccine.

In addition, Reuters recently reported that Pfizer and BioNTech plan to launch human trials of a universal coronavirus vaccine by year's end.

A Variety of Variants

It appears that vaccine manufacturers, who said at the VRBPAC meeting that they've gambled and already begun producing bivalent BA.1 boosters to be ready to meet the fall demand, will continue to collect data about those shots while developing BA.4 and BA.5 boosters.

The FDA has advised the companies that they should submit data from clinical trials of modified vaccines containing an Omicron BA.1 component prior to authorization of a bivalent vaccine containing a BA.4-BA.5 component.

"Manufacturers will also be asked to begin clinical trials with modified vaccines containing an Omicron BA.4-5 component, as these data will be of use as the pandemic further evolves," Marks said in the June 30 FDA announcement.

Moderna will continue to submit data to the FDA about mRNA-1273.214, its experimental bivalent vaccine containing mRNA-1273, which is its prototype COVID-19 vaccine, and a BA.1 spike protein component, a company spokesperson said in an email.

The mRNA-1273.214 vaccine "has demonstrated a superior neutralizing antibody response against Omicron and a potent response against subvariants BA.4 and BA.5," she said. "We are simultaneously developing a bivalent booster vaccine candidate that

specifically targets Omicron subvariants BA.4 and BA.5."

A Pfizer spokeswoman told *JAMA* in an email that "our mRNA [messenger RNA] platform allows us to quickly update our vaccine constructs…."

The fate of BA.1 bivalent vaccines that have already been manufactured "at risk" isn't clear.

"[W]e are working collaboratively to identify pragmatic solutions to address the evolving pandemic and to minimize wastage as we prepare to potentially shift toward a variant-adapted vaccine if authorized," the Pfizer spokesperson said.

For now, though, Offit is of the "if it ain't broke, don't fix it" school of thought when it comes to COVID-19 vaccines. "We might be able to live with these ancestral strain" vaccines, he said.

A healthy 71-year-old, Offit contracted COVID-19 for the first time about a month ago.

Even though he received no treatment, he had mild symptoms for only a couple of days, which, he says, shows that the 3 doses of a prototype vaccine he's received (he figures a second booster might have extended his protection against COVID-19 infection by 6 months) did exactly what they were supposed to do—keep him from getting seriously ill.

"That's a win," Offit said. ■

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Conflict of Interest Disclosures: Besides his current VRBPAC and previous ACIP memberships, Dr Bernstein serves as a consultant for the ACIP COVID-19, influenza, and combined immunization work groups. Besides coinventing the technology used to create Corbevax, for which he has not received any royalty income to date, Dr Hotez has written several books for which he does receive royalties.

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