COVID-19 Vaccine Makers Plan for Annual Boosters, but It’s Not Clear They’ll Be Needed

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Millions of people in the US and other countries have already received an additional COVID-19 vaccine dose months after their primary vaccination. In the parlance of US Food and Drug Administration (FDA) and US Centers for Disease Control and Prevention (CDC) officials, these doses are booster shots, a term that suggests they’ll need to be regularly repeated to maintain protection against SARS-CoV-2 infection. In fact, Moderna and Novavax, a Maryland company whose COVID-19 vaccine isn’t available in the US, have announced they’re working on combination COVID-19 and seasonal influenza shots, which would make an annual booster against SARS-CoV-2 more convenient.

But Will It Be Necessary?

Most vaccines are 2, 3, or 4 doses and done, except for influenza and tetanus and diphtheria vaccines. Influenza viruses change enough each year to necessitate annual flu shots—note that they’re not called boosters—modified to target the circulating strains. And although the World Health Organization doesn’t recommend tetanus and diphtheria boosters, the CDC advises getting them every decade (a 2020 study, however, suggested that tetanus and diphtheria boosters are unnecessary).

Only time will tell whether COVID-19 vaccines require periodic boosting. “The bottom line is that we don’t know,” Anthony Fauci, MD, director of the National Institute of Allergy and Infectious Diseases, said in a recent interview. “My feeling is what happens in the next 8 to 10 months is going to be very telling.”

COVID-19 vaccines were designed to protect against serious illness from SARS-CoV-2 infection, so to track whether their effectiveness wanes over time, “We’ll be looking at deaths, we’ll be looking at hospitalizations, we’ll be looking at various gradations of disease,” explained Fauci, who at a September briefing said it was likely that full protection would require 3 vaccine doses.

Increasing numbers of fully vaccinated individuals becoming seriously ill with COVID-19 would suggest immunity has waned and another booster is needed, he told JAMA.

Define Fully Vaccinated

Some scientists believe that the evidence shows people are fully vaccinated after just 2 doses and that the so-called boosters now recommended for many people in the US, the United Kingdom, Italy, France, Germany, and Ireland accomplish little more than “polishing the immune response of the lucky ones,” as Giovanna Borsellino, MD, PhD, professor of immunohematology at Rome’s Santa Lucia Foundation, put it in an email. With SARS-CoV-2 “galloping freely” in lower-income countries where few people have been vaccinated, she said, “this is scientifically irresponsible and morally unacceptable.”

The billions needed to pay for booster shots for all US adults, as pledged by the Biden administration in August, might provide a bigger bang for the buck if spent on other policies, such as improving vaccine uptake among the 1 in 5 American adults who haven’t received a single dose or reselling or donating doses to countries that don’t have enough first or second doses to go around, authors from Harvard Medical School noted in a recent opinion piece.

But some scientists argue that the first 2 doses of the mRNA COVID-19 vaccines can’t be expected to provide long-lasting immunity because they were administered only 3 or 4 weeks apart. The third dose represents completion of the primary vaccine regimen, not a booster, the thinking goes.

“When we rolled the 2 mRNA [messenger RNA] vaccines out, we spaced them pretty close together. We did that because we were in dire straits. The issue with that is when you space them so close together, you don’t get long-lasting protection,” Peter Hotez, MD, PhD, professor of immunohematology at the National Institute of Allergy and Infectious Diseases, said in an interview. “When we gave those first 2 doses so close together, we basically bought ourselves a 3-dose vaccine.”

According to the CDC’s “General Best Practice Guidance for Immunization,” “As a general rule, decreasing the interval between doses in a multiple-dose vaccine
series may interfere with antibody response and protection." Hotez noted that the immune response soars higher and more quickly after a third mRNA vaccine dose administered 8 months after the second dose than it does after the first 2 doses administered only a few weeks apart.

It’s unlikely that annual doses will be necessary, however, 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. "I think there’s a high probability that it could be 3 [doses] and done."

Given that the earliest clinical trial participants received COVID-19 vaccines only about a year and a half ago, predicting how long the immunity they elicit will last is difficult. However, experience with other vaccines and recent studies examining the durability of the immune response to COVID-19 vaccines so far provide clues.

Long Memory

One of the main arguments for COVID-19 vaccine boosters has been the observation that anti-SARS-CoV-2 antibodies wane over time, which has been seen with other vaccines. While antibodies are relatively easy to assess, the assays aren’t yet standardized, and scientists haven’t yet determined how low titers can go and still be protective—known as a correlate of immunity.

In addition, neutralizing antibodies are only 1 component of the immune system. "Luckily, the immune system has multiple layers of protection," Akiko Iwasaki, PhD, an immunobiologist at the Yale University School of Medicine and the Howard Hughes Medical Institute, said in an interview. White blood cells called memory T and B cells stand guard for years, ready to mount a defense, including generating antibodies, against a particular antigen should it ever appear or reappear. Memory cells “are quickly recruited to the site of infection,” Iwasaki explained. “They quickly respond by making more clones of themselves, so they start to fight back.”

It’s those memory cells that keep people infected with SARS-CoV-2 out of the hospital, noted Paul Offit, MD, director of the Vaccine Education Center at Children’s Hospital of Philadelphia.

“To prevent serious illness, all you really need is immunological memory. If you look at COVID vaccines, that is holding up,” said Offit, a member of the FDA’s Vaccines and Related Biological Products Advisory Committee, which recommended that the agency authorize emergency use of boosters of all 3 COVID-19 vaccines available in the US. “I think the premise for giving booster doses is thin.” On November 19, the FDA authorized both mRNA vaccines as a booster for people aged 18 years or older who’ve been fully vaccinated.

Much of the evidence for booster shots has come from Israel, the first country to push them. “Disease rates started to come down,” Offit noted. “Israel claimed it was because of their boosters.” However, he pointed out, COVID-19 rates had also begun falling around the same time in the US, which had not yet begun offering booster shots.

A recent study by Borsellino and her co-authors backs Offit up. The researchers monitored T-cell and antibody responses to the SARS-CoV-2 spike protein in 71 healthy health care workers and scientists for up to 6 months after they received the first of their 2 BNT162b2 (Pfizer-BioNTech) COVID-19 vaccine doses.

The study found that vaccination induced a sustained T-cell response. “I think that the cellular response induced by the vaccines has all the prerequisites to last a lot longer than 6 months,” Borsellino noted.

“Of course, one would wish to have high-stereotyping antibody titers forever, and this is not the case for these vaccines,” she added. “But the clinical data clearly show that protection from severe disease remains high.”

She and her coauthors now have data for up to 10 months after the first vaccine dose, which confirm a persistent T-cell response, Borsellino said. “Our data, and that of others, overlap with what is known from other successful vaccines, even if they are not for respiratory viruses.”

Outside of a research study, it’s not possible for vaccinated individuals or their physicians to accurately determine whether immunity has waned, short of becoming seriously ill with COVID-19. The FDA has authorized emergency use of a number of antibody tests, but the agency advises that they shouldn’t be used to evaluate immunity to SARS-CoV-2, especially after vaccination.

And in March, the FDA authorized emergency use of Adaptive Biotechnologies’ T-Detect COVID Test to assess the T-cell response in people who suspect they previously might have been infected with SARS-CoV-2. However, Adaptive Biotechnologies notes on its website, “The clinical significance of a positive or negative result following COVID-19 vaccination has not been established, and the result from this test should not be interpreted as an indication or degree of protection from infection after vaccination.”

As Iwasaki explained, “We don’t know if a ‘yes’ [positive result] means you’re protected or a ‘no’ [negative result] means you’re not protected.”

Still, Fauci holds out hope for the possibility of standardized, at-home test kits to measure neutralizing antibodies in a drop of blood, given that the technology already exists. “It’s not going to be a perfect science,” he noted, “but I think as time goes by, we’ll get better and better tests.”

Great Expectations

Emerging data consistently show that vaccine effectiveness against asymptomatic and mild COVID-19 infections declines over time, although protection against disease severe enough to require hospitalization generally remains high, the World Health Organization noted recently.

“In general, you don’t find people in intensive care [with COVID-19] who have been vaccinated,” Norman Baylor, PhD, a former director of the FDA’s Office of Vaccines Research and Review, said in an interview. “So we know the vaccines are working.”

For many individuals, though, protection against severe COVID-19 isn’t good enough—an attitude that appears to help drive the demand for boosters.

Of course, no one wants to be sick and miss work, school, or social activities. But, Offit said, there’s another reason people want to avoid even the mildest of COVID-19 symptoms: They’re worried about developing long COVID—symptoms that persist for weeks or even months after the acute disease phase.

“You can get long COVID from even a mild infection,” Iwasaki noted. “I think that fear is justifiable.”

Only a few studies have investigated the likelihood of vaccinated individuals experiencing long COVID after becoming infected with SARS-CoV-2. A recent study of 1497 health care workers in Israel who were fully vaccinated with BNT162b2 found that only 39 of them had documented SARS-CoV-2 breakthrough infections, most with mild or no symptoms. However, 7 or 8 had symptoms that lasted more than 6 weeks, including a persistent loss of smell, cough, and fatigue.
Another recent study collected self-reported data from 8400 community-based adults in the United Kingdom who had confirmed SARS-CoV-2 infection after their first or second COVID-19 vaccination. Compared with a control group of unvaccinated infected individuals, infected individuals who had 2 doses of vaccine were about half as likely to experience symptoms for 28 days or more. Trial participants had been vaccinated with BNT162b2, mRNA-1273 (Moderna), or ChAdOx1-S/nCoV-19 (AstraZeneca), which isn't available in the US.

And a study using US Department of Veterans Affairs (VA) electronic health care databases, which was posted November 15 before peer review had been completed, found that among people with confirmed COVID-19, those who had been vaccinated were less likely than those who weren't to experience postacute sequelae, including death. However, among the 16 035 vaccinated individuals with COVID-19, including those who had not been hospitalized during the acute phase, the risks of death and postacute sequelae were slight but not trivial, the authors noted. Maintaining vaccine effectiveness by optimizing vaccine schedules and boosters and employing nonpharmaceutical interventions such as masking may reduce breakthrough infections and, therefore, lower the risk of long COVID-19, the authors concluded.

Aspiring to prevent even the sniffles from SARS-CoV-2 infection sets the bar higher for COVID-19 vaccines than for other vaccines, Iwasaki, Offit, and Fauci agreed. "We've never asked influenza vaccines to do that," Fauci said. "You can't expect a vaccine to protect you completely from getting infected." However, people hospitalized with seasonal influenza were less likely to experience any type of sequelae than vaccinated individuals hospitalized with COVID-19, the VA study found.

Poor public health messaging that erroneously lumps together asymptomatic and serious infections hasn't helped lower the public's expectations of COVID-19 vaccines, Offit said.

For example, he noted that news reports about fully vaccinated Supreme Court Justice Brett Kavanaugh recently testing positive for COVID-19 often described him as having a "breakthrough" infection, implying that the vaccine had failed to do its job, even though he was asymptomatic.

And when President Joe Biden said in an August 18 speech that a booster was the best way to protect against SARS-CoV-2 variants that might arise, "he just told the nation that you're not fully vaccinated unless you get a third dose," Offit said.

Boosters vs Variants?
A few panelists at the recent FDA advisory committee meetings to discuss third doses of mRNA-1273 and BNT162b2 COVID-19 vaccines questioned why the manufacturers didn't consider updating their so-called boosters to target the Delta variant—now responsible for virtually all SARS-CoV-2 infections worldwide—much the same way seasonal influenza vaccines change each year.

In response, Moderna Senior Vice President Jacqueline Miller, MD, told committee members October 14 that her company is investigating vaccines targeting SARS-CoV-2 variants instead of the wild-type, or original Wuhan-Hu-1, SARS-CoV-2 isolate. For now, though, mRNA-1273 and BNT162b2 boosters are the same as the first 2 shots (although Moderna’s is half the dose), which are based on the SARS-CoV-2 spike protein of Wuhan-Hu-1.

So far, though, the SARS-CoV-2 vaccines seem to be holding up against the Delta variant.

In a recent study, Iwasaki and her coauthors analyzed the development of anti-SARS-CoV-2 antibody and T-cell responses in 40 health care workers who had received 2 doses of the mRNA-1273 or BNT162b2 vaccine. Some of the participants had previous SARS-CoV-2 infection.

The researchers collected blood samples from trial participants 6 times, ranging from before vaccination to up to 98 days after the first dose, and exposed the samples to 16 different SARS-CoV-2 variants, including Delta.

Overall, the health care workers' blood retained neutralization capacity against all variants, although samples from previously infected individuals displayed overall better neutralization capacity than did blood from individuals who had never been infected.

The findings point "to vaccine boosters as a relevant future strategy to alleviate the impact of emerging variants on antibody neutralizing activity," Iwasaki and her coauthors wrote. □

Conflict of Interest Disclosures: Dr Baylor serves as president and chief executive officer of a regulatory consulting firm that provides strategic advice to much of the pharmaceutical industry, including COVID-19 vaccine manufacturers. Dr Hotez is an inventor of COVID-19 vaccine technology owned by the Baylor College of Medicine that was recently licensed nonexclusively to several companies in Asia and Africa for production of a low-cost recombinant protein vaccine. He is also the recipient of numerous grants supporting his research on vaccines against COVID-19 and other infectious diseases. Dr Iwasaki reports serving as a consultant for RIGImmune and Xanadu. Drs Borsellino, Fauci, and Offit report no disclosures.

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