Despite Its Fan Base, Newly Authorized “Traditional” Novavax COVID-19 Vaccine Is Having Trouble Gaining a Foothold in the US

Rita Rubin, MA

To say that Krystal Lashley went to great lengths to get the Novavax COVID-19 vaccine (NVX-CoV2373) would be a gross understatement.

In April, Lashley traveled roughly 3700 miles from her home in Metuchen, New Jersey, to a pharmacy in Paris, France, for her first dose. She then flew to the UK, where she stayed with relatives before returning to Paris a month later for her second dose of NVX-CoV2373.

After writing about her journey on social media, Lashley said, she received numerous requests for help from other people in the US who wanted or were required by their employer to get vaccinated against COVID-19 but, for various reasons, chose not to get either of the messenger RNA (mRNA) shots available to them. Lashley had done her homework and knew which countries that had already authorized NVX-CoV2373 would provide it to nonresidents.

She shut down her ad hoc vaccine travel agency after the US Food and Drug Administration (FDA) on July 13 authorized NVX-CoV2373 for emergency use as a 2-dose primary COVID-19 vaccine in adults 18 years or older. Six days after the FDA acted, the US Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) issued an interim recommendation about the use of NVX-CoV2373.

“For those waiting for a COVID-19 vaccine built on a different technology, now is the time to get vaccinated,” CDC Director Rochelle Walensky, MD, PhD, tweeted after endorsing the ACIP recommendation.

Lashley had done her homework and knew which countries that had already authorized NVX-CoV2373 would provide it to nonresidents.

Ideology vs Technology

The BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) COVID-19 vaccines are the first ever of any vaccines on the market to use mRNA technology, although scientists had been working on mRNA vaccines against other diseases for decades. These vaccines introduce the mRNA blueprint for the SARS-CoV-2 spike protein to the cells of the body, which make copies of it, stimulating an immune response. The cells then tear up the mRNA blueprint into harmless pieces, which are then excreted in waste from the body.

But misinformation and disinformation that spread on social media led some people to wrongly believe that mRNA vaccines altered recipients’ DNA or contained microchips to track their movements. Other people hesitated to get vaccinated because they viewed the mRNA vaccines as too new, and, therefore, unproven. Still others, including Lashley, wanted to get vaccinated but had contraindications to using the mRNA vaccines.

Novavax has tried to capitalize on people’s unfamiliarity with mRNA vaccines by emphasizing that NVX-CoV2373 vaccine uses “a tried and true approach,” John Beigel, MD, associate director for clinical research in the Division of Microbiology and Infectious Diseases at the National Institute of Allergy and Infectious Diseases (NIAID), noted in an interview. However, he said, there aren’t yet data that support the notion that NVX-CoV2373’s efficacy or safety is superior to that of the mRNA vaccines.

NVX-CoV2373 is a protein subunit vaccine, adjuvanted to enhance the immune response. Instead of providing instructions to cells on how to make the SARS-CoV-2 spike protein, NVX-CoV2373 contains pieces of the spike protein to trigger an immune response. Protein-plus-adjuvant vaccines have been on the US market for about 30 years and include shots that protect against human papillomavirus; shingles; and diphtheria, tetanus, and pertussis. In a pivotal phase 3 trial, NVX-CoV2373 was found to be safe, with 90.4% efficacy—comparable with the findings of the phase 3 trials leading to Emergency Use Authorization (EUA) for...
BNT162b2 and mRNA-1273. (One advantage of NVX-CoV2373 is that it can be stored in a refrigerator, unlike the mRNA vaccines, which require storage in extremely cold temperatures.)

At the June 7 meeting convened to discuss whether the FDA should grant EUA to NVX-CoV2373, Jay Portnoy, MD, the consumer representative on the agency’s Vaccines and Related Biological Products Advisory Committee (VRBPAC), expressed skepticism that his unvaccinated acquaintances would change their minds with the introduction of a non-mRNA vaccine.

“[T]heir hesitation is more ideological than technological, so I really doubt that this vaccine is going to crack that nut,” said Portnoy, a professor of pediatrics at Children’s Mercy Hospital in Kansas City, Missouri.

“Novastans”
A Fortune article in January described what it called NVX-CoV2373’s “cultlike” following, its members dubbed “Novastans.”

“We have a fan club,” Gregory Glenn, MD, president of research and development at Novavax in Gaithersburg, Maryland, acknowledged in an interview with JAMA.

Lashley, who is 38 years old, didn’t become a Novastan because she distrusted mRNA vaccines. She has asthma, so she was looking forward to getting vaccinated against COVID-19 as soon as possible. But after receiving her first dose of the BNT162b2 vaccine in April 2021, she said, she experienced anaphylaxis, a rare adverse event. (A recent systematic review found that out of 84 case reports of people who had an anaphylactic reaction to an mRNA vaccine, 69 had a prior history of asthma or allergy, as Lashley did.)

Her physician advised her to wait until NVX-CoV2373 became available until receiving another vaccine dose. “He told me it’s a traditional vaccine,” she explained.

Lashley says she didn’t expect she’d have to wait more than a year for a non-mRNA option. As she puts it, she lived “in a bubble” for months. Her employer, a medical software company for whom she works in accounts receivable, allowed her to continue to work remotely. She’d socialize only in her backyard.

Finally, she decided she could wait no longer. She was planning a wedding celebration in her husband’s home country of Guyana, where the COVID-19 rate has been high, according to the CDC. She first thought about getting vaccinated in the UK, since her relatives lived there, but she discovered that country didn’t yet have doses to administer. Then she decided to set up her home base with her UK relatives and fly to Croatia for the shot, but she missed her flight out of Heathrow. On the spur-of-the moment, she opted to get vaccinated in Paris. In case she had an allergic reaction to NVX-CoV2373, she picked a pharmacy near a hospital; she has a Certificat de Vaccination to show for her efforts.

She and other Novastans criticized the FDA on social media for not moving more quickly to authorize the shot. After all, they argued, Novavax had submitted its request to the FDA for an EUA on January 31, 2022, and the vaccine was developed with the help of government funds—$1.6 billion from Operation Warp Speed. In addition, more than 3 dozen countries had already authorized the use of NVX-CoV2373, beginning with Indonesia on November 1, 2021, and, by the time the FDA authorized it, approximately 4 million doses had been injected into arms worldwide, according to Novavax.

Who’s Left?
Novastans’ vociferousness may have belied their small numbers. Although the US government has purchased 3.2 million doses of NVX-CoV2373, enough to vaccinate 1.6 million people, only 11,990 doses had been administered as of August 17, according to the CDC Data Tracker.

“In the case of the US, I believe we were late to the market, and US vaccination was driven by what was available and shown to work, mRNA vaccines,” Novavax Chief Executive Officer Stanley Erck said during the company’s second quarter financial results conference call on August 8.

In an interview with JAMA, VRBPAC member Paul Offit, MD, said he doubted that many unvaccinated individuals will rush to get a more traditional vaccine such as NVX-CoV2373. After all, he noted, earlier in the pandemic, some unvaccinated people said they were waiting for the mRNA COVID-19 vaccines to win full approval, not just an EUA. But even when that happened, Offit said, vaccine holdouts didn’t rush to roll up their sleeves and get the shots.

Besides, given that hundreds of millions of individuals worldwide have received mRNA COVID-19 vaccines, “how much more information do you need at this point” about their safety and efficacy? asked Offit, director of the Vaccine Education Center at Children’s Hospital of Philadelphia and coinventor of a vaccine against rotavirus. “The data are in at this point.”

As for people who still aren’t vaccinated, Offit said, “you either are a science denier or you live in a world where you believe you are never going to die from this virus.”

In an email to JAMA, Kathleen Neuzil, MD, MPH, director of the Center for Vaccine Development and Global Health at the University of Maryland School of Medicine, echoed Offit’s comments. “We have a robust safety database with the mRNA vaccines, given the magnitude of the vaccination effort,” she said. “[T]he unvaccinated will be a hard group to convince for any vaccine.”

Results of a survey conducted from June 18 to June 23, 2022, of a representative sample of 1,788 unvaccinated adults bear her out. Only 10% overall said they would “definitely” or “probably” get a traditional protein-based COVID-19 shot if the FDA authorized one, found Morning Consult, an online survey research company.

Their reasons for not getting a protein-based vaccine were remarkably like those often cited in regard to mRNA vaccines. Nearly three-quarters of the unvaccinated adults said they were concerned about adverse effects, while two-thirds said they were worried the vaccine moved through clinical trials too fast. A quarter of them said they were generally against vaccines.

Boosting Use
Considering how many adults have already received their primary COVID-19 vaccinations and how few of those who haven’t are expected to get NVX-CoV2373, the protein-plus-adjuvant shot might end up playing a bigger role in the US as a booster and as a primary vaccine for adolescents, who have a lower vaccination rate than adults. Other countries have already authorized the vaccine for both of those indications, and on August 19, the FDA authorized emergency use of NVX-CoV2373 for adolescents 12 years through 17 years of age in the US. Novavax also recently launched an international clinical trial of NVX-CoV2373 as a primary vaccination series and booster in children 6 months through 11 years of age.

Novavax announced August 15 that it has applied to the FDA for an EUA of NVX-CoV2373 as a booster after a primary series of the vaccine (homologous booster) or any
other vaccine (heterologous booster) in adults 18 years of age or older.

Six weeks earlier, the FDA had recommended that booster vaccines include a component of the now-dominant Omicron BA.4 and BA.5 variants—which spike proteins are identical—this fall and winter.

At the June 28 VRBPAC meeting to discuss the makeup of fall COVID-19 boosters, Glenn presented data showing that NVX-CoV2373 boosters for people who’d previously received that vaccine or had been infected with SARS-CoV-2 produced broad cross-neutralizing antibodies against a variety of SARS-CoV-2 variants, which he described as a "universal-like" response, capable of dealing with whatever the virus might throw at it.

In a preclinical study involving macaques, there was no difference between NVX-CoV2373 and a bivalent vaccine containing NVX-CoV2373 plus an Omicron component, he said. Still, Novavax launched a clinical trial in May to compare the antibody responses of NVX-CoV2373 with 2 experimental vaccines—a monovalent Omicron BA.1 vaccine and a bivalent vaccine combining the monovalent vaccine with NVX-CoV2373. “We have to do what the customer wants,” Glenn explained, referring to the federal government, even though it’s “not clear what to do from a public health standpoint.”

In Japan—which in April became the first country in the world to approve NVX-CoV2373 for both primary and booster immunization—and Australia, many people who initially had received mRNA vaccines are choosing NVX-CoV2373 boosters, Glenn told JAMA.

Australia provisionally registered NVX-CoV2373 as a booster on June 9, 2022. Four weeks later, the Australian Technical Advisory Group on Immunisation (ATAGI) recommended that either of the mRNA COVID-19 vaccines be used as a booster regardless of which vaccine had been used for the primary series. However, the Novavax vaccine can be used as a booster dose for people who have a contraindication to or prefer not to get mRNA COVID-19 vaccines, the ATAGI said.

A booster dose of NVX-CoV2373 roughly 6 months after a primary series of the vaccine produced much higher neutralizing antibody titers than the peak achieved after the first 2 doses, according to a randomized clinical trial posted online by Lancet Infectious Diseases on August 10. The trial, funded by Novavax and the Coalition for Epidemic Preparedness Innovation, found that the immune response after the booster was at least as high as that found in the phase 3 trials of the primary 2-dose vaccine series, against both the prototype SARS-CoV-2 and variants that were evaluated, including Omicron BA.1.

The authors of an accompanying editorial noted that in places with a high primary vaccination rate, NVX-CoV2373 will probably be used to boost people who previously had received another vaccine. A UK trial published in December evaluated the immunogenicity of NVX-CoV2373 and 6 other vaccines given as heterologous boosters 10 to 12 weeks after completion of a primary series of either BNT162b2 or ChAdOx1 nCoV-19 (Oxford-AstraZeneca), which is not authorized for use in the US. The study, funded by the UK Vaccine Taskforce and the UK National Institute for Health Research, found that NVX-CoV2373 boosted immunity, as measured by anti-spike antibodies and neutralizing assays, after primary vaccination with either BNT162b2 or ChAdOx1 nCoV-19. However, the T-cell-boosting effect of NVX-CoV2373 was lower in people who had received a primary series of BNT162b2 than it was in those who had previously received 2 doses of ChAdOx1 nCoV-19.

Still, the perception that NVX-CoV2373 is a better booster might spur people who previously received mRNA vaccines to seek out the new shot, even though “I can’t think of any reason that, theoretically, [NVX-CoV2373] would be better” than an mRNA booster, Beigel said.

Although the vaccine isn’t yet authorized as a booster for anyone in the US, “some people I’ve been talking to are going to another state to get around that,” figuring there won’t be a record of their primary vaccination, Lashley said.

“I will be getting my third shot with or without the FDA’s approval,” she said. “I’ve already learned not to wait on them.”

Published Online: August 24, 2022. doi:10.1001/jama.2022.13661
Conflict of Interest Disclosures: Dr Glenn, president of research and development at Novavax, holds stock in the company.
Note: Source references are available through embedded hyperlinks in the article text online.