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New COVID-19 vaccines are in late-stage trials

For now, only the Pfizer and Moderna vaccines have full FDA approval, but many candidates are in phase 2 or 3 trials.

by **ROSANNA SUTHERBY, PHARM.D.**

The emergence of the SARS-CoV-2 virus in late 2019 prompted drug manufacturers, biotechnology companies and laboratories to swing into action to develop agents that would neutralize the virus and prevent death, hospitalization and symptomatic disease from COVID-19. Much was riding on developing a safe and effective vaccine, and by the summer of 2020, 28 companies had candidates in clinical trials, and 13 of those had advanced to phase 3 studies. The companies with early contenders included major pharmaceutical companies — Pfizer and BioNTech, Johnson & Johnson, Sanofi, Merck, AstraZeneca — and smaller biotech companies such as Moderna and Novavax. Several of these candidates have since gained full approval or emergency use authorization in various parts of the world.

By the end of 2020, the Pfizer and Moderna vaccines had emerged as the strongest candidates; if the initial vaccine development were a race, they were the gold and silver medalists. They were the first to gain emergency use authorization from the FDA for the prevention of COVID-19 disease in adults. Comirnaty, the brand name of Pfizer-BioNTech's vaccine, was authorized for emergency use by the FDA on Dec. 11, 2020, and received full approval on Aug. 23, 2021, for use in people 16 years and older. It is also authorized for emergency use in children 5 to 15 years old and is awaiting emergency use authorization by the FDA for children 6 months through 4 years old. Spikevax, the brand name of the vaccine developed by Moderna, was authorized for emergency use on Dec. 18, 2020, and gained full FDA approval for use in adults 18 years and older on Jan. 31, 2022. The Johnson & Johnson vaccine followed the Pfizer and Moderna vaccines out of the pipeline and into use. The FDA granted the Johnson & Johnson vaccine an emergency use authorization on Feb. 27, 2021. It has not yet received full FDA approval.

With the availability of various types of vaccines throughout the world and the emergence of new variants, the COVID-19 vaccine pipeline looks quite different today than it did in 2020. According to *The New York Times*' Coronavirus Vaccine Tracker, there are 114 COVID-19 vaccine candidates in clinical studies. Of those, 48 are in phase 3 or combined phase 2 and 3 trials. The up-and-comers include messenger RNA (mRNA), protein-based, viral vector and inactivated coronavirus vaccines.

mRNA Vaccines

The Pfizer and Moderna vaccines are mRNA vaccines that carry the RNA instruction for making the spike protein that provokes an immune response. Arcturus Therapeutics in San Diego and Duke-NUS Medical School in Singapore have partnered to develop three self-amplifying mRNA vaccine candidates — ARCT-021, ARCT-154 and ARCT-165. The vaccines are in various stages of phase 1 through phase 3 trials. Preliminary data recently released by Arcturus suggest that ARCT-154 and ARCT-165 may produce an antibody response to effectively neutralize SARS-CoV-2 and several variants, including omicron. Arcturus intends to apply for emergency use authorization in the United States and Singapore.

In Asia, the Academy of Military Medical Sciences, Abogen Biosciences and Walvax Biotechnologies have joined efforts to develop what may potentially be China's

first mRNA vaccine. The vaccine candidate ARCoV is in phase 3 trials. The companies are also testing a potential booster vaccine in a separate phase 3 trial.

Protein-based vaccines

Protein-based vaccines use part of the virus to prime the immune system. In the case of the protein-based COVID-19 vaccines, the vaccines use the spike protein that juts out from the surface of the SARS-CoV-2 virus. A protein-based COVID-19 vaccine would offer an alternative for people who are worried about the new mRNA vaccine technology. They would be made using the same methods as some widely used vaccines, such as the one that protects against hepatitis B and pneumococcal infections.

Novavax developed a protein-based vaccine containing nanoparticles studded with genetically engineered coronavirus spike proteins that the immune system recognizes. The vaccine, known as NVX-CoV2373, Covovax and Nuvaxovid, is stable for three months at refrigerated temperatures and is given by intramuscular injection as a two-dose series, three weeks apart.

In phase 3 trials, NVX-CoV2373 demonstrated 90.4% efficacy in preventing COVID-19 symptoms and 100% efficacy in preventing severe disease. It has received emergency use authorization from the World Health Organization, the European Union and other countries.

On Jan. 31, 2022, Novavax applied for an emergency use authorization in the United States. The company will continue to extend its phase 3 trials to test for vaccine boosters.

Viral vector vaccines

Viral vector vaccines use a modified version of a virus other than SARS-CoV-2 to ferry DNA instructions for making the SARS-CoV-2 telltale spike protein. Vaxzevria, the brand name of the vaccine developed by researchers at the University of Oxford in England and produced by AstraZeneca, contains coronavirus spike-producing instructions in DNA carried inside an adenovirus. Although this vaccine was among the early contenders, it has not gained authorization for use in the United States. It is fully approved for use in adults in Brazil and India and authorized for emergency use in the European Union. Problems with data reporting have impeded the vaccine from authorization for use in the United States.

Another viral vector vaccine of interest is an oral vaccine developed by Vaxart, a San Francisco biotech company. The Vaxart candidate is currently in a phase 2 trial. The company is testing its vaccine in unvaccinated volunteers and also in vaccinated adults to see if it might be used as a booster.

Other noninjectable COVID-19 vaccines in the pipeline include a repurposed oral polio vaccine, several intranasal vaccine candidates and a vaccine with a transdermal delivery mechanism. These agents are primarily in phase 1 and phase 2 trials. If they succeed in moving through the pipeline, they will be a welcome alternative for people with an aversion to needles.

Inactivated coronavirus vaccine

Inactivated vaccines are made using viruses or bacteria that have been killed by heat, radiation or chemicals. Although they cannot cause disease, the body can recognize the antigens and mount an immune response. Valneva, a French company, has created the only inactivated coronavirus vaccine developed in Europe. The vaccine candidate, called VLA2001 for now, can be stored at refrigerated temperatures, and it is given as two intramuscular injections separated by four weeks. In a phase 3 trial conducted in the United Kingdom, VLA2001 produced an immune response 40% higher than that produced by Vaxzevria. However, more recent laboratory results suggest that VLA2001 is not as effective against the omicron variant as it is against other variants. If those results hold up, that limitation may cloud the future of the Valneva vaccine.

Variant-specific vaccines

As variants continue to emerge, several companies have expanded research on the efficacy of their current vaccines against circulating variants, especially omicron. On Jan. 25, 2022, Pfizer-BioNTech enrolled the first participants in a trial comparing the safety and efficacy of a new omicron-specific vaccine with its current one. The trial is meant to determine if a variant-specific vaccine can produce an immune response at least as strong as the currently available vaccine and perhaps with a longer duration.

The next day, Moderna started a phase 2 study of an omicron-specific booster. Moderna said the trial is designed to compare the safety and efficacy of its omicron-specific booster candidate with two doses of its current vaccine and a three-shot series that also includes the current booster. Moderna is also evaluating a multivalent booster that would be

designed to combat more than one variant at a time.

Who dropped out?

As numerous companies set forth unprecedented efforts to develop safe and effective vaccines quickly, a few emerged as front-runners while others abandoned their projects. Sanofi and Merck had initially received federal support for the development of their vaccines but have since discontinued their research. Sanofi and Translate Bio collaborated in 2020 in the development of a mRNA vaccine. However, by the time they had results from trials, the Pfizer and Moderna vaccines were widely available. Sanofi decided to cease efforts on the mRNA vaccine production but is continuing phase 3 trials on a protein-based vaccine that may be used as a booster.

Merck worked with two organizations, Themis Bioscience, an Austrian company, and IAVI, a nonprofit group devoted to developing vaccines, in 2020 on separate projects to develop an injectable and an oral vaccine against COVID-19. Merck abandoned the development of both vaccines because neither produced a more robust immune response than that produced by natural infection. Instead, the company partnered with Johnson & Johnson to help produce their vaccine.

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FOURTH SHOT IS RECOMMENDED FOR THE IMMUNOCOMPROMISED

Getting boosted is now the rule, not the exception, when it comes to COVID-19 vaccination recommendations. The CDC now recommends that everyone, ages 12 and older, get a dose of an mRNA COVID-19 vaccine, either Pfizer's or Moderna's. For people who have gotten the two-shot Pfizer or Moderna series, the booster is their third jab. For those who got the single-dose Johnson & Johnson vaccine, it is the second.

But for people who are immunocompromised — people in active cancer treatment, for example — to be fully boosted means a fourth dose. Early last month, the CDC's Advisory Committee on Immunization Practices recommended that people who are immunocompromised get a fourth dose of vaccine at least three months after the last dose of a three-dose series of shots. The CDC is calling the third shot for people who immunocompromised a third primary shot, not a booster. It doesn't recommend the Johnson & Johnson vaccines for those who are immunocompromised.

The CDC says that about 2.7% of the adult population in the U.S. are immunocompromised. People who are immunocompromised are more likely to experience a severe case of COVID-19 and also a prolonged one.

A number of news outlets have reported that some pharmacies have turned away immunocompromised patients seeking a fourth shot, even though it is recommended by the CDC. Under what is known as emergency use instructions the CDC has the authority to make these guideline revisions, independent of the FDA once a product has been approved.

The updated recommendations are based on evidence that people who are immunocompromised have a stronger immune response when a fourth dose is administered one to three months after the third dose. The most recent guidance clarifies that immunocompromised patients should receive a three-dose primary series, with a fourth dose considered the booster.

For people who are not immunocompromised, the recommended sequence remains a primary series comprising two doses followed by a third, the booster.

The CDC's Advisory Committee on Immunization Practices has also recommended that healthcare providers can, on a case-by-case basis, administer additional doses of the Pfizer or Moderna vaccines outside of the FDA and CDC dosing intervals "based on clinical judgement when the benefits of vaccination are deemed to outweigh the potential and unknown risks."