the immune system — and by vaccines.

The targets of molnupiravir and Paxlovid are different, but researchers will still need to show that the drugs work against variants, says Mellors. Merck has done laboratory studies indicating that molnupiravir is effective against Delta and other variants — including the Beta lineage, which was first identified in South Africa.

Could the coronavirus become resistant to antivirals?

Drug resistance is a familiar problem and is the reason that some viral infections, such as HIV and hepatitis C, are treated using combinations of antivirals. "The bottom line is that we're going to need combination therapies," says Katherine Seley-Radtke, a chemist who is developing antiviral drugs at the University of Maryland, Baltimore County.

So far, molnupiravir and Paxlovid have been tested only as single therapies.

It will be important to look at people who don't respond to molnupiravir or Paxlovid, to find out whether viral resistance is a factor, says Douglas Richman, an infectious-disease specialist at the University of California in San Diego. Researchers should also closely monitor people who receive the drugs and have weakened immune systems. Because infections might last longer in these people, there could be more opportunity for resistance to emerge, says Richman.

Who will be able to access the new drugs?

Merck has signed an agreement with the Medicines Patent Pool to provide the intellectual-property licences needed to produce molnupiravir in low- and middle-income countries. Gore says that the patent pool is in discussions with Pfizer. Both companies have committed to tier pricing to allow lower- and middle-income countries to pay less for the antivirals.

But wealthy countries are already placing large orders, raising concerns that their stockpiles will limit access in other parts of the world. The situation is all too familiar, says John Amuasi, leader of the Global Health and Infectious Diseases Research Group at the Kumasi Centre for Collaborative Research in Tropical Medicine in Ghana. "Look at what's happened with the vaccines."

By Heidi Ledford

News explainer

HOW PROTEIN-BASED COVID VACCINES COULD CHANGE THE PANDEMIC

Jabs from Novavax and other biotech firms are coming. Scientists say they have a lot to offer.

By Elie Dolgin

Pamela Sherry is eager to become immunized against COVID-19. But she has put off getting a jab.

"I believe vaccines work," she says. "I want the protection." But she is prone to acute immune reactions and has blood-circulation problems, so she is concerned about the shots available in the United States, where she lives — those based on messenger RNA and viral-vector technologies. Although safe for most of the population, these vaccines have been linked to rare but potentially severe side effects that could be a risk for Sherry, including heart inflammation and blood clots.

So she has been waiting for the menu of vaccine options available to her to expand. In particular, she is holding out for a vaccine built from purified viral proteins. Unlike the relatively new technologies that the mRNA and viral-vector COVID-19 shots are based on, protein vaccines have been used for decades to protect people from hepatitis, shingles and other viral infections. To elicit a protective immune response, these shots deliver proteins, along with immunity-stimulating adjuvants, directly to a person's cells, rather than inserting a fragment of genetic code that the cells must read to synthesize the proteins for themselves.

"Protein vaccines are going to beckon in a new era of COVID-19 immunization."

Although protein vaccines are not yet in widespread use against COVID-19, late-stage clinical-trial data so far look promising, demonstrating strong protection with few side effects. If such a shot were available, "I would go and get it right away," says Sherry, who runs a stationery business from her home in Prosper, Texas.

Sherry's wait could soon be over. After months of quality-control setbacks and manufacturing delays, executives at biotechnology firm Novavax in Gaithersburg, Maryland, say they are poised to submit the company's long-awaited application for its protein-based vaccine to US drug regulators before the end of the year. Meanwhile, two vaccine makers in Asia — Clover Biopharmaceuticals, based in Chengdu, China, and Biological E in Hyderabad, India — are similarly on track to file with various national authorities in the coming weeks and months.

In a few corners of the world — Cuba, Taiwan, and elsewhere — home-grown protein shots are already playing a part in vaccination efforts. Now, a wave of such products could allay the fears of vaccine hold-outs such as Sherry, serve as booster shots and, importantly, help to fill a void in the global pandemic response.

"Protein vaccines are going to beckon in a new era of COVID-19 immunization," says Nick Jackson, head of programmes and innovative technologies at the Coalition for Epidemic Preparedness Innovations, which has invested more than US$1 billion in five protein-based COVID-19 vaccines in active development.

Intrinsically slow

From the earliest days of the pandemic response, researchers anticipated that protein-based designs would be slower off the blocks than other vaccine technologies.

Companies know how to manufacture gobs of purified protein on a large scale — using genetically engineered cells from mammals, insects or microbes — but the process involves many steps, each of which has to be optimized to make a specific protein. "There's an intrinsic slowness," says Christian Mandl, a former industry executive who now consults on vaccine-development issues. Most of the protein-based vaccines currently in testing have been crafted around some version of the coronavirus SARS-CoV-2's spike protein, which helps the virus to enter cells (see 'Protein vaccines 101').

Large-scale trials by Novavax and Clover have already yielded efficacy data. According to a preprint published last month (which has not been peer reviewed), the Novavax jab offered more than 90% protection against symptomatic COVID-19 in a 30,000-person study completed early in the year — before the Delta variant arrived, when only milder forms of the virus were in circulation (L. M. Dunkle *et al*. Preprint at medRxiv https://doi.org/g5w9; 2021).

Clover reported lower efficacy results for its protein-based jab — just 67% for symptomatic

COVID-19 of any severity – but that number was probably deflated, because the vaccine was tested on populations grappling with more virulent strains of SARS-CoV-2, including the Delta variant. Both vaccines elicited antibody levels on a par with those induced by mRNA shots, which have emerged as some of the most efficacious in the pandemic.

The results show that making COVID-19 vaccines using proteins "is not a substandard approach just because it took longer", says Ryan Spencer, chief executive of Dynavax Technologies of Emeryville, California, which makes the Clover vaccine's adjuvant.

The shots also seem to be safe. None of the 50 or so protein-based COVID-19 vaccines now in clinical testing around the world have elicited any major side effects. Even many of the reactions typically elicited by the mRNA or viral-vector jabs – headaches, fevers, nausea and chills – have proved much less common with the protein-based alternatives.

"That's going to allow a lot of people not to fret as much," says Cindy Gay, an infectious-disease physician at the University of North Carolina School of Medicine in Chapel Hill, who co-led testing of the Novavax vaccine.

But even if one protein-based vaccine succeeds – both in terms of its performance and in finding a market – there's no reason to think they all will.

For one thing, the form of the spike protein they deploy varies greatly from one product to the next. Some use single proteins, others groups of three. Some use full-length spike protein, others just a fragment.

Many of them are also manufactured using different types of cell. Novavax and a vaccine produced by drug giants Sanofi and GlaxoSmithKline (GSK) synthesize proteins using cells from a moth called the fall armyworm (*Spodoptera frugiperda*); Clover and Taiwan's Medigen Vaccine Biologics Corporation, based in Taipei, rely on hamster ovary cells, a mainstay of therapeutic-antibody production in the biotechnology industry. Plus, the leading candidates rely on different adjuvants, each of which prods the immune system in its own way, resulting in different kinds of vaccine response.

All of this could translate into different efficacy and safety profiles, says Thomas Breuer, chief global health officer for GSK. "I could imagine that you will see differences, but time and the phase III trial results will give us the ultimate answer."

Those results have the potential to shape booster programmes in wealthy countries, where large percentages of the population have already been vaccinated. Although mRNA jabs are currently being used as boosters in many of these places, tolerability concerns could drive people to seek out protein-based boosters once they're available.

Plugging the equity gap

Once authorized, protein shots are also expected to rapidly address supply shortages that have plagued efforts to vaccinate lower-income countries. Novavax and Clover, for example, have each pledged that next year, they will donate hundreds of millions of doses of their jabs to COVAX, an initiative designed to distribute vaccines around the world.

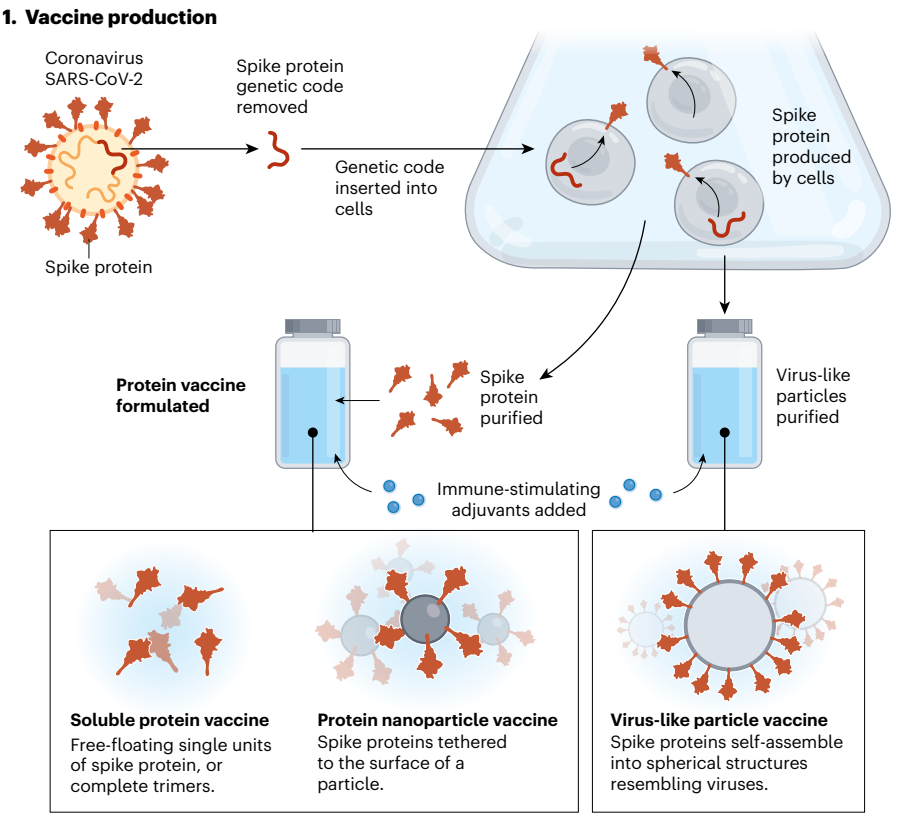
The global health community has also been arguing that equitable access to COVID-19 vaccines could be achieved by manufacturing shots locally in the global south. To achieve this, more researchers should be looking to simple, inexpensive production systems that manufacturers in less-wealthy countries can readily implement, says Christopher Love, a chemical engineer at the Massachusetts Institute of Technology in Cambridge.

Biological E is already taking advantage of a system based on yeast to manufacture the vaccine it licensed from Baylor College of Medicine in Houston, Texas. According to Maria Elena Bottazzi, a Baylor virologist who helped to create the product, that makes it "probably the easiest and cheapest to scale" of all the COVID-19 vaccines on or nearing the market today.

In the earliest days of the COVID-19 crisis, vaccine platforms such as mRNA brought the advantage of speed, says Ralf Clemens, a vaccine-industry veteran and a scientific adviser to Clover. But the coming wave of protein-based vaccines will have a lot more to offer, he says. In the long run, when it comes to protecting the world against coronavirus infections, "I think they will prevail."

PROTEIN VACCINES 101

There are a number of ways to formulate a protein-based COVID-19 vaccine, including using free-floating protein or tethering protein to a nanoparticle. Many vaccines are based on the coronavirus's spike protein, but some use only a key part of the protein, called the receptor-binding domain.



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