COVID antiviral pills: what scientists still want to know

Molnupiravir and Paxlovid could change the course of the pandemic if clinical-trial results hold up in the real world.

SERGEI SUPINSKY/AFP VIA GETTY

Antiviral drugs molnupiravir and Paxlovid can cut COVID-19 hospitalizations.

'Tis the season of the antiviral. In just over a month, two antiviral drugs — both capable of being taken as a pill — have been found to cut COVID-19 hospitalizations and deaths in clinical trials of people treated soon after their initial infection.

On 4 November, the United Kingdom became the first country to approve molnupiravir, which was developed by Merck, based in Kenilworth, New Jersey, and Ridgeback Biotherapeutics in Miami, Florida. The approval came just over a month after the companies announced that the antiviral drug, which will be branded Lagevrio, halved the risk of hospitalization in people with mild or moderate forms of COVID-19. A day after the UK approval, Pfizer, based in New York City, announced that its antiviral drug Paxlovid cut hospitalizations by 89%.

Previous antiviral options against COVID-19 were expensive and had to be administered in a hospital. The new drugs are relatively cheap to manufacture and can be taken at home. "For large parts of the world that have not got good vaccine coverage, this is really a godsend," says Charles Gore, executive director of the Medicines Patent Pool, a United Nations-backed organization based in Geneva, Switzerland, that works to increase access to medicines.

The new antivirals have the potential to reshape the course of the pandemic. *Nature* looks at five key factors that could determine their success.

How effective are the new antivirals?

Judging from the press releases, both drugs can slash hospitalizations from COVID-19 when they are given soon after infection.

Researchers will be looking at the ages and ethnicities of those who were enrolled in the trials, and at any other health conditions that they had, says John Mellors, an infectious-disease specialist at the University of Pittsburgh Medical Center in Pennsylvania.

Because antiviral drugs often need to be given early in the course of an infection, Mellors will also be looking for more detail about when the drugs were given in the trials, and at how those timings correlated with efficacy. Neither trial had enough participants to enable firm conclusions to be drawn about the drugs' ability to prevent deaths, but no deaths occurred in their treatment arms.

Researchers are also keen for any clue — including from further clinical trials — as to whether the drugs affect transmission of the coronavirus, or prevent illness in people who have been exposed to it.

If they do, the combination of vaccines and antiviral drugs could become a powerful tool, says Jerome Kim, director-general of the International Vaccine Institute in Seoul. "It opens up some new possibilities for the way we think about control."

Are the treatments safe?

Both antivirals were well tolerated by study participants, and potential side effects were minor. But both drugs have features that could limit who would be able to take them.

Molnupiravir acts by introducing mutations into the viral genome during viral replication. A metabolite of the drug is picked up by a viral enzyme called RNA-dependent RNA polymerase and incorporated into the viral genome, eventually causing so many errors that the virus can no longer survive.

Human cells have a DNA, rather than an RNA, genome. But one laboratory study has suggested that molnupiravir could cause mutations in human DNA as well (S. Zhou *et al*. *J. Infect. Dis.* **224**, 415–419; 2021).

A full course of treatment with molnupiravir is only five days long. But regulators might be cautious, particularly when it comes to treating pregnant individuals, says Kim.

Paxlovid acts by inhibiting an enzyme that's needed to process some viral proteins into their final, functional form. The drug is a combination of an antiviral, dubbed PF-07321332, and another drug called ritonavir, which helps to prevent enzymes in the liver from breaking down the antiviral before it has a chance to disable the coronavirus. It can affect how some other medications are metabolized by the body, including some that are commonly used to treat heart conditions, suppress the immune system and reduce pain.

This means that many people might not be able to tolerate the combination of PF-07321332 and ritonavir. But physicians might find ways to work around some drug–drug interactions.

Will the drugs work against variants of concern?

In theory, the drugs should be effective against known coronavirus variants, including Delta. These variants are mainly characterized by mutations in the viral spike protein and other regions that are targeted by

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