NEW COVID DRUGS FACE DELAYS AS TRIALS GROW MORE DIFFICULT

Fewer people are eligible for the massive studies needed to test treatments for severe COVID-19.

By Saima May Sidik

After two years of breakneck research, scientists have amassed a collection of therapies to treat people with COVID-19. But now, researchers fear that the development of new treatments could falter as the clinical trials needed to test them become increasingly difficult.

Vaccinations in many places have led to a decline in severe disease, shrinking the pool of potential study participants. Hesitance to enrol in trials is rising, and the existence of potent treatments is making statistical analysis more difficult, too.

"It was definitely easier to do research in the past. Now you've got to design a study that meets the standards of care doctors want to do, and patients want to do. And it's a lot harder," says Elizabeth Hohmann, an infectious-disease expert at Massachusetts General Hospital in Boston.

More than half a dozen COVID-19 therapies have been recommended by the World Health Organization (see 'Virus-taming tools'). Some cut the risk of death for those already in hospital. Others lower the odds of having to be hospitalized at all. Death rates are dropping in some countries that are fortunate enough to have access to these treatments.

But, in many areas, the available therapies are limited in supply and high in cost. There's also the looming spectre of resistance to antivirals such as the blockbuster Paxlovid (nirmatrelvir-ritonavir), developed by Pfizer in New York City. Researchers worry that progress in establishing new treatments will stall, even as many people are left without treatment options.

Shrinking pool

Thanks largely to vaccines, certain hard-hit countries have seen death rates drop precipitously. In Brazil, for example, where deaths were once running at 3,000 a day, the figure has fallen to below 200 a day. Yet that welcome news can complicate trials.

In the pandemic's early days, health researcher Edward Mills at McMaster University in Hamilton, Canada, and his colleagues set up a trial in Brazil to study drugs to prevent serious outcomes of COVID-19. When they launched the trial, called TOGETHER, in early 2020, the share of study participants who eventually died or had to be hospitalized was 16%. But the number dropped to 3–5% after vaccines became available.

Before they could continue testing whether certain drugs prevent severe outcomes, the organizers therefore had to enrol more people who were in danger of becoming critically ill. That meant expanding the trial to further sites — in South Africa, Pakistan and elsewhere.

Another type of hesitancy

Scientists also worry that even those people who do qualify for trials are more reluctant to take part than they would have been at the beginning of the pandemic. When Hohmann began overseeing a trial called ACTT to test COVID-19 treatments in early 2020, recruitment was quick: ill people had no better option. The trial quickly enrolled 1,062 people and soon showed that the antiviral drug remdesivir prevents death[1].

But Hohmann says that, as effective treatments such as remdesivir were rolled out, it became more difficult to recruit participants for subsequent trials. Many people feel safer with the established regimen, which today includes remdesivir and the steroid dexamethasone, than they do adding an experimental drug.

"It just takes a much more adventurous person to step onto that third drug," Hohmann says. Hesitance of another sort might have affected a Canadian clinical trial for the drug losartan as a treatment for severe COVID-19. The majority of people in Canada became vaccinated during 2021, so most of the people available to join the losartan trial were unvaccinated. That could explain the rise in the share of people who were invited to join the study but declined: 18% in mid-2021 and 35% by the end of the year[2].

Statistical complexity

As treatments have multiplied, so too has the complexity of the statistical calculations needed to determine a drug's effectiveness. This shift has already affected the PRINCIPLE trial, which tests whether drugs can speed recovery of infected UK residents.

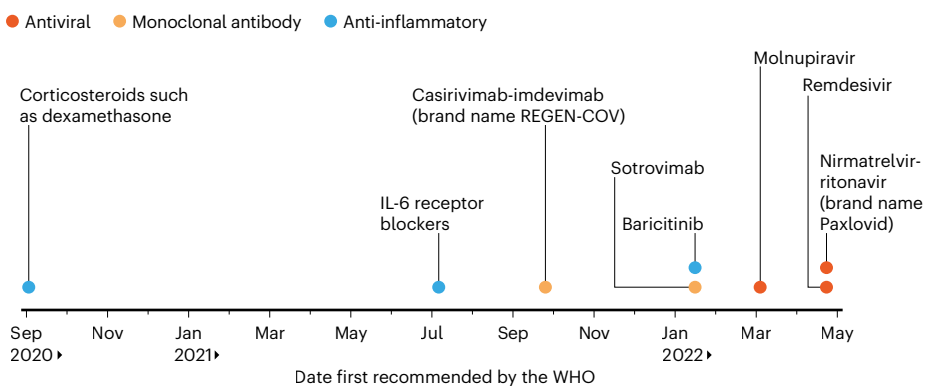
Doctors caring for study participants are free to prescribe treatments in addition to the drug being tested. That dilutes any difference in outcome between participants taking the placebo and those taking the treatment under study, says Ly-Mee Yu, a medical statistician at the University of Oxford, UK, and PRINCIPLE's lead statistician. Smaller differences mean that researchers need to work with larger groups of participants, and trials therefore take longer.

Hohmann notes that if researchers want to compare a new, highly effective drug against Paxlovid, the potent antiviral that is now the leading treatment for early COVID-19, they will need to recruit a huge number of trial participants to discern a statistically significant difference between the two treatments. "You'd have to have a real game-changer to take on Paxlovid," she says.

But researchers might need to embrace the difficulties of finding a Paxlovid challenger. Recent experiments on cells[3] suggest that Paxlovid-resistant strains of the virus might arise — a stark reminder that no matter how complex the playing field becomes, the virus is defining the rules of the game.

VIRUS-TAMING TOOLS

The virus that causes COVID-19 was identified only in early 2020, but the World Health Organization (WHO) has already recommended more than half a dozen treatments for the disease. Still other therapies have been recommended by domestic agencies such as the US National Institutes of Health.



WORLD HEALTH ORGANIZATION; US NATIONAL INSTITUTES OF HEALTH

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