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# The hunt for drugs for mild COVID: scientists seek to treat those at lower risk

**People who are unlikely to develop severe COVID-19 have no widely approved medications to ease the illness.**

Saima May Sidik



A worker in protective garb administers a COVID-19 test in Shanghai, China. Credit: Hugo Hu/Getty

A shift is afoot in the search for COVID-19 therapies: some researchers are turning their attention towards drugs that could be used to treat mild illness, even in people who are not at high risk of severe disease.

Such drugs could fill a yawning gap, says infectious-disease expert Oriol Mitjà at Germans Trias i Pujol University Hospital in Barcelona, Spain. High-risk people have treatment options, he says, but moderate-risk people who don't quite qualify for existing treatments are left fearing for their safety. "There is a need there," he says. Such treatments could reduce the disruption that even mild cases can inflict on people's jobs and family lives.

Political hurdles and recruitment issues have dissuaded some researchers from shifting their focus away from severe disease, but others are pushing ahead. "This could still be really important – to look at decreasing time spent ill," says Susanna Naggie, an infectious-disease clinician at Duke University School of Medicine in Durham, North Carolina.

## **The cupboard is bare**

The World Health Organization (WHO) recommends more than a half-dozen COVID-19 drugs for people who either have severe disease or are at risk of hospitalization. The WHO cautions against several drugs as treatments for mild illness – but makes no recommendations of what to take instead.

Treating sore throats and sniffles might sound indulgent, but drugs for mild disease could mark a turning point in the pandemic. Such a treatment not only would get people back to their lives sooner, but could also limit disease spread. Fewer infections mean fewer opportunities for the virus to mutate, so drugs for mild disease could stem the rise of new variants.

Low-income countries could also benefit. For example, in the Democratic Republic of Congo, only 3.3% of the population has received a vaccine dose. But drugs could help to compensate for low vaccination rates, says Frédéric Monnot, a drug-development researcher at the Drugs for Neglected Diseases Initiative in Geneva, Switzerland.

Many drugs are easier to deploy in Africa than vaccines, which often require cold storage and must be administered by trained personnel.

## Not just a luxury

Immunologist Marc Feldmann at the University of Oxford, UK, points to another benefit: researchers don't fully understand the risk factors that lead to severe disease. Widely used treatments for mild disease could save the lives of people who do not know that they are at high risk. "The reality is that everybody is at risk," he said.

Naggie and her colleagues started recruiting participants for a trial called ACTIV-6 in early 2021, when vaccination was becoming widespread and it looked like the pandemic was trending toward less severe disease. Instead of focusing on treating people with risk factors, ACTIV-6's organizers have leaned into this new phase of the pandemic.

The researchers recruit anyone 30 years old or older – including vaccinated individuals – to study whether [existing drugs, such as fluvoxamine, now used to treat depression, can help people to get through COVID-19](#). The researchers consider whether therapies resolve recipients' symptoms sooner, helping them to get back to their lives faster, rather than limiting their analysis to prevention of hospitalization or death. Neither [the antiparasitic drug ivermectin](#) nor the asthma drug fluticasone sped recovery under the conditions the team tested. The scientists have recently finished enrolling people for their trial of fluvoxamine.



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Although ACTIV-6 tests repurposed drugs, Feldmann and his colleagues think a new type of antiviral could treat mild COVID-19. Most viruses need sugar molecules to take on their 3D shapes, and they use their hosts' biochemical machinery to mould these molecules into a usable form. Modified sugars called iminosugars can gum up this machinery and disrupt the formation of viral particles.

Feldmann, who is developing iminosugars, says they could limit the disease course and viral reproduction and spread, making them good candidates for treating mild COVID-19. Because they interrupt host molecules instead of targeting the virus directly, they are unlikely to spur resistance. “It’s exactly what the patients want,” he said.

The drug company Emergent BioSolutions, in Gaithersburg, Maryland, recently tested the safety profile of iminosugars, clearing the way for clinical trials. Biochemist Raymond Dwek, who is also at the University of Oxford and involved in developing iminosugars, says such trials could be completed within two years.

## Drug barriers

But there are barriers to finding drugs for mild disease. Among them are treatment guidelines — published by organizations such as the WHO — that focus on severe disease, says Edward Mills, a health researcher at McMaster University in Hamilton, Canada. If guidelines don’t encourage doctors to prescribe drugs for mild disease, research into such drugs is unlikely to be useful, says Mills, who is also a principal investigator of the TOGETHER trial, aimed at finding existing affordable drugs to treat COVID-19.

The guidelines’ silence on mild disease, he says, has disincentivized him from widening his focus. Naggie, who is a member of the US National Institutes of Health committee on COVID-19 treatment guidelines, hopes trials such as ACTIV-6 prompt guideline committees to broaden their approach.

Researching mild disease is feasible in only some parts of the world, points out Monnot, who is involved in the ANTICOV trial, which seeks treatments for mild and moderate COVID-19. In Africa, where ANTICOV is running trials, people are unlikely to seek help for mild COVID-19, or even recognize the symptoms. That makes recruiting people in low-risk categories difficult. “In Africa, when they have fever, they’re not feeling well, the first thing they are thinking is about malaria,” he says.

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for non-severe COVID-19<sup>1</sup>. Both had engendered broad interest on the basis of initially promising results.

Despite difficulties and setbacks, Naggie thinks that it is important to continue working to find drugs to treat mild COVID-19, both because of broad public-health benefits and because long quarantine periods disrupt many people's lives. "We need to make sure that we reflect that as we move forward with clinical trials in this space," she said.

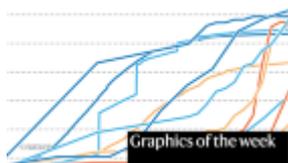
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