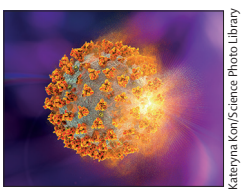
The role of antiviral treatment in the COVID-19 pandemic



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For the **Paxlovid results** see https://www.pfizer.com/news/press-release/press-release-detail/pfizer-announces-additional-phase-23-study-results

For the **molnupiravir trial** see *N Engl J Med* 2021; published online Dec 16. DOI:10.1056/NEJMoa2116044

For the **remdesivir studies** see *N Engl J Med* 2020; **383:** 1813–26 and *N Engl J Med* 2021; published online Dec 22. DOI:10.1056/NEJMoa2116846

On Dec 22, 2021, the US Food and Drug Administration (FDA) issued an emergency use authorisation for Pfizer's COVID-19 antiviral, Paxlovid. Trial results released by the manufacturer indicate that the drug cuts the risk of hospitalisation or death for high-risk patients by 88%, compared with the placebo, if given within 5 days of symptom onset. A second oral antiviral, Merck Sharp & Dohme's (MSD) molnupiravir, received FDA authorisation on Dec 23. In a phase 3 study of 1433 patients with mild-to-moderate COVID-19 and at least one risk factor for severe illness, treatment with molnupiravir within 3 days of symptom onset reduced the chances of hospitalisation or death by 30%, compared with the placebo.

Remdesivir has already been shown to shorten recovery times in hospitalised patients with COVID-19. Trial results published last month showed that it is also effective earlier in the disease course. Treatment with remdesivir within 7 days of the appearance of symptoms reduced the chances of hospitalisation or death by 87%, compared with the placebo, for non-hospitalised patients with COVID-19 who were at high risk of severe disease. But the drug has to be administered intravenously, which drastically limits its utility, especially in patients who would otherwise be expected to isolate at home.

Pfizer and MSD have both struck agreements with the Medicines Patent Pool (MPP) allowing dozens of low-and-middle-income countries around the world to access Paxlovid and molnupiravir. MSD has separately signed licensing agreements with several generics manufacturers. Charles Gore, executive director of the MPP, expects that the generic version of molnupiravir will initially be sold for around US$20 in the 105 countries included in the deal with the MPP.

"The oral antivirals do not have the complications of the monoclonal antibodies, which have to be given in hospital, and they are a lot less expensive", Gore told *The Lancet Respiratory Medicine*. "They are very well suited to low-and-middle-income countries." Predicting demand will be tricky, but Gore reckons that the MPP has licensed enough suppliers to minimise the potential for shortages.

Molnupiravir is simple to manufacture, and so for a while at least is likely to be the most widely available antiviral for COVID-19. Paxlovid is a more complicated product. It is a combination of two drugs: ritonavir plus the novel protease inhibitor PF-07321332. The two drugs work in different ways. Molnupiravir prompts an accumulation of errors in the replicating virus, until the virus can no longer survive. Paxlovid blocks a protease required for the process of replication. Paxlovid's results are more promising than those for molnupiravir, though they have yet to be published in the scientific press. France responded to the publication of the full results from the molnupiravir study by cancelling an order of 50 000 doses of the antiviral—the interim results had suggested molnupiravir halved the risk of hospitalisation.

"There is a good chance we will be able to drive down the cost of molnupiravir to $10 per course; that is a great price for a 30% reduction in hospitalisation", commented Gore. The US Government has agreed to pay around $530 per course of Paxlovid, and $700 per course of molnupiravir. On Jan 4, 2022, Indian pharmaceutical firm Dr Reddy's Laboratories announced that it would sell a course of its version of molnupiravir for 1400 rupees (US$18·85).

Charlotte Summers, professor in intensive care medicine at the University of Cambridge (Cambridge, UK), welcomed the advent of the oral antivirals. But she pointed out that there are still questions over the role they are likely to play in combating the pandemic. The phase 3 trials for both molnupiravir and Paxlovid recruited unvaccinated individuals who were at high risk of hospitalisation for COVID-19. "We do not have many of these people left in the UK", noted Summers. "We do not know what the outcome of these drugs will be in vaccinated populations, or whether they will provide benefit to patients who are not at high risk for severe illness." There are plenty of unvaccinated people in low-and-middle-income countries. But for antivirals to be effective, treatment has to be started promptly. This will be problematic in places with limited access to diagnostics.

Moreover, Paxlovid is associated with several drug–drug interactions, which could complicate its use in the community. There are concerns that molnupiravir could potentially affect bone and cartilage growth; the FDA authorisation does not extend to people under the age of 18 years.

The PANORAMIC trial will look at the effectiveness of several COVID-19 antivirals in high-risk patient populations in the UK. The majority of participants are likely to be vaccinated. A substudy within the trial will examine whether the antivirals prevent transmission of SARS-CoV-2. The investigators began recruitment last month for a study into the effectiveness of early treatment with molnupiravir. As yet, there are no clinical studies combining molnupiravir and Paxlovid. "We really need to be looking at combination therapies", said Summers. "It is hard enough to come up with effective antivirals; we have to do all we can to prevent the development of resistance."

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