Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

The future of Paxlovid for COVID-19

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For **Bourla's comments to Bloomberg** https://www.bloomberg.com/news/newsletters/2022-05-04/pfizer-s-advice-for-when-paxlovid-isn-t-enough-take-more

For **John Farley's remarks** see https://www.fda.gov/drugs/news-events-human-drugs/fda-updates-paxlovid-health-care-providers

For the **long COVID preprint** see https://www.researchsquare.com/article/rs-1617822/v1

In comments to Bloomberg published on May 3, 2022, Pfizer chief executive officer Albert Bourla suggested that patients who experience a relapse of symptoms after finishing a course of the company's COVID-19 antiviral, Paxlovid, should take a second course of the drug. Yet the emergency use authorisation issued by the US Food and Drug Administration (FDA) stipulates that Paxlovid is "not authorized for use longer than five consecutive days". On May 4, John Farley, director of the Office of Infectious Diseases at the FDA, reiterated this message. "There is no evidence of benefit at this time for a longer course of treatment… or repeating a treatment course of Paxlovid in patients with recurrent COVID-19 symptoms following completion of a treatment course", stated Farley.

The US Government pays around US$530 for each 5-day course of Paxlovid. The drug is a combination of ritonavir plus the novel protease inhibitor PF-07321332. The emergency use authorisation was granted late last year, on the strength of results from the phase 2–3 trial showing that Paxlovid reduces the risk of hospitalisation or death for high-risk patients by 88%, compared with the placebo, if given within 5 days of symptom onset. The trial only recruited unvaccinated individuals. But three-quarters of the UK population and two-thirds of the US population are now fully vaccinated against COVID-19.

"It is clear that antivirals have an important role early in the course of illness for people whose immune systems are not working well, or who have not responded well to the vaccine", said Charlotte Summers, professor of intensive care medicine at the University of Cambridge (Cambridge, UK). "We still do not have evidence on whether Paxlovid prevents hospitalisation or severe illness in people who have been vaccinated." The UK-based PANORAMIC trial is examining the use of antivirals in patients who have not been hospitalised, regardless of vaccination status. On April 12, Paxlovid was added to the trial.

On April 29, Pfizer released results from a phase 2–3 study examining post-exposure prophylaxis with Paxlovid. The study concluded that the use of the antiviral does not significantly reduce confirmed and symptomatic infection with SARS-CoV-2 in adults exposed to the virus through a household contact. Michael Peluso is assistant adjunct professor in the division of experimental medicine at the University of California, San Francisco (CA, USA). He pointed out that post-exposure prophylaxis with Paxlovid would be difficult to put into practice, even if the drug were shown to be of benefit.

"A lot of exposures to SARS-CoV-2 are not obvious", Peluso told *The Lancet Respiratory Medicine*. "Paxlovid is associated with some bothersome side-effects. Based on what I am hearing from patients, it is probably not something that would end up being widely prescribed when there is no confirmed infection, although we really do need easy-to-take options for post-exposure prophylaxis, particularly for high-risk exposures."

Peluso is co-author of a case series involving three patients with long COVID who have received Paxlovid. The paper has not been peer-reviewed. Two of the patients reported that the antiviral therapy improved the symptoms of long COVID. In the third case, the patient developed long COVID despite taking Paxlovid for acute infection with SARS-CoV-2. "It is only relatively recently that people with long COVID have been getting reinfected with SARS-CoV-2, and so have been eligible for treatment with Paxlovid under the FDA authorisation. Some people report that their long COVID symptoms have improved or resolved", said Peluso.

Whether or not antivirals will relieve long COVID hinges on the extent to which the condition is attributable to viral persistence. "At the moment, there is not enough evidence to support antiviral therapy for long COVID", stressed Summers. "There have been reports that the genetic material from the virus has lingered in the guts of previously infected people, but we still do not know if this is live virus." She added that symptoms of long COVID, such as blood clots and cardiovascular effects are indicative of a dysregulated host immune response, rather than viral persistence. "There could be some deep tissue persistence of hard-to-find virus that is driving a dysregulated inflammatory immune response", countered Peluso. "I think there is enough compelling preliminary data to study this systematically." The issue will only be resolved in large scale studies.

6 months have now elapsed since the FDA authorisation of Paxlovid, yet supplies to low-income settings remain suboptimal. "We have to work harder to ensure equitable access across the world", said Summers. "It worries me that we could potentially be giving antiviral therapy for COVID-19 to patients in the UK or USA who are at low risk of hospitalisation, and who have been fully vaccinated, while there are large numbers of people who need them but have no access to these drugs."

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