Covid-19: Stockpiling antivirals risks repeating Tamiflu mistakes, experts warn

The UK government has made a huge investment in antivirals to fight covid, but some experts are concerned the waste and overspending of the 2000s will recur. Gareth Iacobucci reports

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The government’s Antivirals Taskforce has procured more antivirals per population than any other country in Europe, with over 4.98 million courses ordered so far.1 Included within this is 2.75 million courses of Pfizer’s oral antiviral drug Paxlovid (a combination of nirmatrelvir and ritonavir tablets).

Andrew Hill, senior visiting research fellow in the Department of Pharmacology and Therapeutics at the University of Liverpool, has estimated, using publicly available drug prices in the US, that the UK has spent £2.2bn (€2.6bn; $2.8bn) so far on procuring antivirals. “There’s a vast amount of money involved,” he told The BMJ. “As usual, all government contracts are confidential, so maybe they got some discount. But if the UK paid US prices, which it has with vaccines, then it has spent around £2.2bn on antivirals for covid.”

Uncertain evidence

Yet, despite this huge investment, evidence for the effectiveness of antivirals remains uncertain.

Last November Pfizer reported results from an interim analysis of phase 2/3 data showing that Paxlovid, the second oral antiviral drug for covid-19 to be authorised for use in the UK, can reduce the relative risk of death or hospital admission by 89%.2 The government has seized on these results to justify its investment. However, the data were based on unvaccinated participants, while most at-risk people have already been vaccinated.

Early data indicate that Paxlovid could be more effective than molnupiravir, the first oral antiviral to be made available in the UK, with fewer safety concerns.3 4

The latest rapid recommendation from a WHO Guideline Development Group of international experts, published in The BMJ last week,5 strongly recommended Paxlovid for patients with non-severe covid-19 who are at the highest risk of hospital admission, such as unvaccinated, older, or immuno-suppressed patients. But it made no recommendation for patients with severe or critical covid-19, as there are currently no trial data on Paxlovid for this group. Both studies that informed the recommendation (EPIC-SR and EPIC-HR) excluded patients with severe or critical illness, and all patients were unvaccinated.

The Panoramic trial

The UK’s large national Panoramic study, run by the University of Oxford in collaboration with hubs of general practices, is aiming to fill the gaps in the evidence base by assessing how antivirals work where most of the adult population is vaccinated.

For several months, Paxlovid has been available directly through the NHS to a limited number of people at higher risk of serious illness who test positive for SARS-CoV-2, including those who are immunocompromised, patients with cancer, and people with Down’s syndrome. This month Paxlovid was added to the Panoramic study and will now be offered to an additional 17 500 vulnerable people in England, in addition to the 23 000 previously recruited to the trial to receive molnupiravir.6

Nick Lemoine, medical director at the National Institute for Health and Care Research, which is funding the study, said, “While smaller scale studies have already shown this new antiviral treatment to be highly effective against covid in the early stages of infection, additional evidence from much larger cohorts is needed to enable clinicians and health services to make best use of these exciting new treatments.”

Jumping the gun?

Some experts are concerned that the government has jumped the gun by going ahead with stockpiling antivirals in such quantities when the evidence is still uncertain. Hill said, “If the drug fails in Panoramic, can the UK get the money back? And how do you justify spending a 10th of the entire NHS drug budget on drugs that might not work at all? It could be used much more wisely elsewhere.

“I think there are a lot of parallels with Tamiflu, and it could be a repeat. With Tamiflu [and Relenza] the government wasted £600m. This time we’re talking £2.2bn.”

In a recent editorial published in The BMJ, James Brophy, professor of medicine and epidemiology at McGill University, Montreal, argued that molnupiravir was authorised too early for covid patients and without sufficient evidence of its effectiveness.7 He told The BMJ that although the situation was less clear cut with Paxlovid he held similar concerns.

“There is so much uncertainty as to what is the actual effect size [in the EPIC-SR trial], especially in vaccinated people,” he said.
Brophy attributes the early stockpiling to what he bluntly calls a “‘cover our ass’ mentality, which says, ‘Let’s look like we are doing something even if we aren’t sure it works and it costs a fortune, since we don’t want to be criticised.’”

“No apologies”

When asked by The BMJ whether it would be able to recoup any of the money spent on procuring Paxlovid if the drug was shown not to be effective in the Panoramic trial, the Department of Health and Social Care for England said that details on costs and the recuperation of drugs were commercially sensitive.

A department spokesperson said, “We have secured more lifesaving antivirals per head than any other country in Europe for NHS patients, and we make no apologies for doing so, given that our first priority is protecting patients.

“Both antivirals have been shown to be highly effective in clinical trials, as well as by our renowned medicines regulator. For example, Paxlovid reduced the relative risk of hospitalisation or death due to covid by 88%.

“The Panoramic study is collecting further data on how antivirals work in a vaccinated population, to inform the wider rollout later this year.”

Low uptake

Aside from the evidence for their effectiveness, it is also becoming apparent that supply of antivirals is exceeding demand, casting further doubt on the wisdom of stockpiling the drugs in such large quantities.

Uptake in the UK is modest. NHS England said that around 32 000 patients had received antivirals since December, when they were introduced for people outside hospitals, and that only around 6000 had received Paxlovid as of 9 April. An analysis by Reuters showed that supply of Paxlovid has far outstripped demand in the UK, the US, Japan, and South Korea. Complex eligibility requirements, reduced availability of testing, and potential for drug interactions have all been cited as potential barriers.

Hill noted that the need to administer Paxlovid swiftly after infection was a major practical hurdle.

“You have to start treating within five days the symptoms first appearing,” he said. “You get a lot of people who don’t know if it’s actually covid on the first day. Then you’ve got to get a test, then you’ve got to get a GP appointment at short notice, and then you’ve got to get a prescription. I’d suggest this is very hard for most people.”

He added, “The other very serious issue with this drug is that it could actually cause more harm than good. It contains a booster drug called ritonavir, which causes drug interactions by increasing the concentrations of other drugs. In order for that not to happen, somebody has to have a very detailed review of all the patient’s comediations, which could take ages. That’s yet another barrier to somebody starting this drug.”

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