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NEWS ANALYSIS

Covid-19: UK launches antivirals taskforce to deliver home treatments by autumn

Can the UK vaccine taskforce's success in delivering safe and effective covid vaccines be repeated with new antiviral drugs? **Elisabeth Mahase** looks at the research pipeline

Elisabeth Mahase

The UK government has launched an Antivirals Taskforce to identify treatments to be used at home by people who test positive for SARS-CoV-2 infection, to stop the virus spreading and speed up recovery time.

The taskforce will aim to find at least two effective treatments this year, in either a tablet or capsule form. They will go through clinical trial testing and could be rolled out as early as the autumn, the government has said. The hope is that these treatments could prevent future waves of infections and limit the effect of new viral variants, especially over the winter.

The government's chief scientific adviser, Patrick Vallance, said, "Antivirals in tablet form are another key tool for the response. They could help protect those not protected by or ineligible for vaccines. They could also be another layer of defence in the face of new variants of concern. The taskforce will help ensure the most promising antivirals are available for deployment as quickly as possible."

How will the taskforce work?

England's health secretary, Matt Hancock, said, "Modelled on the success of the vaccines and therapeutics taskforces, which have played a crucial part in our response to the pandemic, we are now bringing together a new team that will supercharge the search for antiviral treatments and roll them out as soon as the autumn."

Details on how the new antivirals taskforce will operate are scarce, but the vaccine taskforce operated by bringing together academia, industry, and government officials together with a ringfenced budget and "clear and dedicated ministerial approval process to govern spending commitments."[1]

The therapeutics taskforce also worked closely with the National Institute for Health Research to "ensure the UK is running large enough trials to get definitive answers to key questions."[2]

A "competition" has been launched to find a chair to lead the latest initiative.

Do antivirals work against respiratory viruses?

Two antivirals are recommended for the treatment of the influenza virus in the UK: oseltamivir (Tamiflu) and zanamivir (Relenza). "Antiviral medicines may be prescribed for patients in 'clinical at-risk groups' as well as any who are at risk of severe illness and/or complications from influenza if not treated," the Department of Health and Social Care for England advises.

However, there has been much controversy over oseltamivir, specifically the mass stockpiling of the drug by many governments after the 2009 H1N1 "swine" flu pandemic and the lack of evidence to support its use.[3] A 2009 Cochrane investigation into the evidence for the treatment found that many of the studies used to support its efficacy were unpublished. The manufacturer, Roche, refused to provide the full data from the studies unless confidentiality agreements were signed, and this led to a public campaign—much of it done through *The BMJ*—to pressure companies into releasing the underlying clinical trial data. The campaign lasted four years and was ultimately successful.[4]

The subsequent Cochrane review that used the newly released data found that both oseltamivir and zanamivir shortened the duration of symptoms of influenza-like illness by less than a day and that oseltamivir did not affect the number of people admitted to hospital.[5] Concerns were also raised over oseltamivir 's harm profile. The World Health Organization recommended restricting its use to severe illness in critically ill hospital patients with confirmed or suspected influenza. Despite this, many countries, including the UK and US, still recommend its use outside this narrow window.

Public Health England disagrees with Cochrane's view that antivirals are ineffective for flu, listing several reasons why.[6] It says that Cochrane did not look at observational data and that it reviewed only randomised controlled trials, in which otherwise healthy people are studied. The agency explicitly tells healthcare professionals that they must not be "deterred from prescribing neuraminidase inhibitor drugs as a result of confusion over efficacy."

Meanwhile, in Japan, the antiviral drug favipiravir has been licensed for treating novel or re-emerging influenza viruses since 2014. The treatment works by inhibiting the RNA polymerase, thus stopping the virus from replicating inside human cells. Baloxavir marboxil, an oral antiviral for the treatment of influenza A and B, is also approved in Japan and the US. In randomised controlled trials favipiravir was found to have a similar time to alleviation of symptoms as oseltamivir. However, baloxavir was associated with greater reductions in viral load one

day after the start of treatment, when compared with placebo or oseltamivir.[7]

What drugs are being investigated for covid-19?

Early in the pandemic a combination of two antiviral drugs, lopinavir and ritonavir (Kaletra), normally used to treat HIV, was investigated for use in patients with covid-19. However, randomised controlled trials published in the *New England Journal of Medicine* and *Lancet* reported no benefit in adult hospital patients.[8 9]

Remdesivir is another drug that was highlighted at the start of the pandemic. Originally created to treat hepatitis C and respiratory syncytial virus in 2009 but found to be ineffective, it was then tested against Ebola virus in 2014. Again, the results were disappointing. Jump forward to 2020, and remdesivir trials began again, this time against covid-19. Initial evidence indicated that it shortened recovery times for severely ill patients in hospital, leading to the US, EU, and UK giving the treatment the green light for rollout. However, WHO's Solidarity trial, which included more than 11 000 adults in 405 hospitals across 30 countries, of whom 2750 were randomly allocated to receive remdesivir, then reported that the drug had little or no effect on mortality at 28 days and did not delay the need for ventilation or shorten patients' stay in hospital. Researchers are now looking at whether remdesivir, if given early, could have any benefit in moderately ill patients.[10]

Favipiravir, mentioned above in relation to its approval in Japan to treat flu, is also being investigated for treating covid-19. In the UK the Principle trial is investigating a range of potential treatments to reduce recovery time and prevent hospital admissions and deaths in older people recovering at home and in other non-hospital settings.[11] In April this year the trial announced it would be adding favipiravir to the list of treatments being tested.

Molnupiravir, a drug that inhibits RNA virus replication, is currently undergoing phase II and III clinical trials involving covid-19 patients both in hospital and not admitted.[12] The trials, being run by Merck, have enrolled just over 600 participants (302 non-hospital and 304 hospital patients) randomised to receive molnupiravir 200 mg, 400mg, 800mg, or placebo twice daily for five days. The trials will determine whether the treatment leads to sustained recovery or reduces hospital admissions or deaths.

Another treatment currently undergoing a clinical trial is PF-07321332, an oral antiviral clinical candidate from Pfizer. The phase I trial has only just started (March 2021), but the company said that the candidate has shown potent antiviral activity in vitro against SARS-CoV-2.[13]

How realistic is the timeline?

Because a small number of antiviral drugs are already undergoing clinical trials, the aim to have two rolled out before the end of the year is possible, although the timeline does seem to rely heavily on the ongoing trials delivering successful results.

Janet Scott, a clinical lecturer in infectious diseases who is leading a trial in Glasgow testing favipiravir, said, "We already have one drug in clinical trial, so, yes, in my view, with concerted effort it is possible to have results by the autumn. We cannot promise a positive outcome, of course; results will be what they will be. Efforts so far to trial oral drugs have been logistically challenging due to prioritising, rightly, vaccine clinical trials and also the hospital based Recovery study. So, with political will it is certainly possible to have current trials finished and new trials set up."

However, Scott added that she would advocate for effort also being put into parallel, "earlier phase clinical trials to keep the pipeline of new drugs moving, rather than focusing all research money on end stage clinical trials."

Correction: On 27 April we amended this story as it originally said the influenza virus was a coronavirus.

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