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COVID UNANSWERED QUESTIONS

What are the latest covid drugs and treatments?

Vaccines have taken up much of the spotlight, but where have we got to with covid-19 treatments, asks **Mun-Keat Looi**—and is there a global standard of care?

Mun-Keat Looi *international features editor*

What are the best treatments for covid-19?

Written in cooperation with the World Health Organization, *The BMJ*'s living systematic review is a meta-analysis comparing the effects of treatments for covid-19,[1] using data from more than 400 randomised clinical trials worldwide.

At the time of writing, it states that systemic corticosteroids (particularly dexamethasone), interleukin-6 receptor antagonists (such as tocilizumab), and Janus kinase inhibitors (such as baricitinib) reduce mortality and have other benefits in patients with severe covid-19, such as reducing the length of hospital stay and the time needed on a ventilator. It also notes that the antivirals molnupiravir (Lagevrio), nirmatrelvir/ritonavir (Paxlovid), and remdesivir (Veklury) have also been shown to be effective against non-severe covid-19.

How has treatment advice changed during the pandemic?

What is considered the "best" treatment continues to change as the pandemic progresses. Where previously the primary aim was to prevent death, the world's exposure to covid-19 now means that outcomes are increasingly viewed in terms of reducing hospital admissions, disease severity, and perhaps even transmission.

Molnupiravir is a case in point. A study published in December 2022 involving 25 000 people confirmed that oral molnupiravir was associated with reduced viral detection and load, and patients recovered around four days more quickly than those who received usual care. However, it didn't reduce hospital admissions or deaths among vaccinated high risk patients, which was the primary outcome the trial was set up to test.[2]

Chris Butler, clinical director of the University of Oxford's Primary Care Clinical Trials Unit and co-chief investigator of the study, tells *The BMJ* that although the trial found no benefit from molnupiravir for its primary outcome (to reduce the likelihood of hospital admission or death), it could have other benefits such as a faster recovery time and reduced follow-up with health services. "This could help to ease the burden on UK health services through the treatment of selected patients at home, during times of high disease burden and pressure on key services," he says.

Janet Scott, clinical lecturer in infectious diseases at the University of Glasgow, says, "The vaccines are now doing their job and reducing the severity of infection in the high risk groups, so the benefit of molnupiravir is now more about time to recovery than reducing hospitalisation." Whether the benefits are worth the £577 it costs for the five day course will depend on whether it reduces the number of people who go on to develop long covid, and those results are still being analysed.

"In my view there are currently two major challenges in covid-19 treatment," adds Scott. "The prevention and treatment of long covid, and the prevention and treatment of acute covid-19 in the highest risk groups including immunosuppressed people. This immunosuppressed group is likely going to require a bespoke study focusing on this issue."

Does the standard of care differ around the world?

Although there are recommended standard treatments for acute covid-19 in line with WHO's advice, huge differences in access mean that countries and regions are not consistent.

"The consistency around the globe is probably not what we would want at this point," says Janet Diaz, who leads clinical management at the WHO Health Emergencies Programme. "Of all the drugs that we have available, the one that's most consistently available and used globally is corticosteroids—what we use for patients who have severe or critical covid-19. But I think for the remainder of the drugs that WHO has recommended—such as interleukin-6 receptor blockers, tocilizumab or baricitinib, and oral antivirals—the availability and access is limited in many low and middle income countries, and that has unfortunately probably impacted their use."

There are many reasons behind this, but the upshot is that with limited access and supplies the cost becomes a major factor, as governments apply more scrutiny over evidence of efficacy. With antivirals, for instance, it comes down to how much a government has invested in buying up the various licensed therapies (mainly Paxlovid and molnupiravir), says Stephen Griffin, reader at the University of Leeds. He points out that the European Union still hasn't approved molnupiravir, which shows mixed efficacy data.

Some places are still widely using drugs that have been shown to be ineffective, such as antibiotics and ivermectin—the latter still commonly used in Brazil, for instance.[3] Butler says that this variation in care can be justified to some extent by different vaccination rates, deprivation and nutrition,

coinfection with other organisms, and problems in accessing modern antivirals. "But overall, I think there's a lot of practice that is still not evidence based going on around the world," he says.

Butler adds, "It's also really important not to assume that the evidence from small trials done by the pharma company translates into evidence at scale in every other context in every other country, particularly since the phenotype of the illness varies so much: covid is a very different illness when the population is vaccinated and when there's a different strain around.

"We've got to do the research to make sure that we are generating evidence from within the context. We need evidence from the intended use population before we start giving out drugs at scale."

He cites inhaled budesonide, a steroid, which does have a benefit in terms of recovery and shows a high probability of reducing the need for hospital admission.[4] "That drug is being used in some places, though it wasn't approved in the UK," he says. "But it is an option in other places."

Why don't we have better data on covid treatments?

"We have few head-to-head trials of medications, or comparisons of different combinations of medications," says Tari Turner, director of the National Covid-19 Clinical Evidence Taskforce at Monash University in Australia. "As a result, we have a small shopping list of effective drug treatment options, and little reliable information to guide decisions about which drugs should be used first or in which sequence or combination they should be used."

Griffin says that the development of direct acting drugs was hampered by the initial response to covid-19, which focused on repurposing existing drugs since that was a faster route. "Back in 2020, we had to try and find any antiviral that worked against this virus—that's why remdesivir and molnupiravir was used, as they had been tried before on different sorts of viruses," he says. "There was data on things like interferon beta combined with lopinavir and ritonavir [having efficacy] in vitro, and there was a paper that showed favipiravir worked, but not very well.

"Basically, everything that was in a fairly bare antivirals cupboard was thrown at it in cell culture. That was fine at the time, as it identified lots of decent hits. But what they didn't do was really carry through the validation process particularly well. And we ended up with things like hydroxychloroquine and ivermectin that, rather than repurposed, were mis-purposed."

Antivirals have become caught up in this confusion because, says Griffin, their pricing in comparison with drugs such as ivermectin means that "some quarters believe that the pharmacy companies are trying to thrust expensive drugs down our throats, rather than use cheap, effective alternatives." The monopoly of western drug companies—Pfizer with Paxlovid, for instance—hasn't helped.

However, Diaz says that big pharma is playing its part. She says that the US Food and Drug Administration's partnership for covid-19 drugs "has a therapeutic pillar, and many partners have been trying to advance on negotiations with manufacturers to have fair, transparent pricing and to secure doses and treatment courses for people in poorer, low middle income countries, and also to increase generic production of products.

"I think next year there will be more generic products on the horizon, which will be associated with better pricing of these drugs—and, I think at that point, more access."

How might treatment advice change further in the coming months?

The BMJ's living systematic review is updated regularly as evidence continues to be published.[1] For instance, in December 2022 the Remap-Cap study of long term (180 day) outcomes in critically ill patients with covid-19 found that the benefit of interleukin-6 receptor antagonists persisted at six months.[5] Martin Landray, professor of medicine and epidemiology at Oxford Population Health, University of Oxford, says that while the results raised the possibility that antiplatelet treatment in patients with severe covid-19 would reduce long term mortality, this was not "conclusive."

"It would be wise to wait for the results of the [10 times larger] study of aspirin in the Recovery trial," he said. "These results, including around 18 months of follow-up, should be available early in 2023, along with the results for four treatments that have previously been shown to reduce 28 day mortality: dexamethasone, tocilizumab [an interleukin-6 receptor antagonist], baricitinib, and monoclonal antibody treatment."

Do you have a "Covid Unanswered Question"? Email mlooi@bmj.com, and we'll try to cover it in a future instalment.

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1 Siemieniuk RAC, Bartoszko JJ, Zeraatkar D, etal. Drug treatments for covid-19: living systematic review and network meta-analysis. *BMJ* 2020;370:. https://www.bmj.com/content/370/bmj.m2980. doi: 10.1136/bmj.m2980 pmid: 32732190

2 Butler C, Hobbs R, Gbinigie O, etalMolnupiravir plus usual care versus usual care alone as early treatment for adults with covid-19 at increased risk of adverse outcomes (Panoramic): an open-label, platform-adaptive randomised controlled trial. *Lancet* 2022 (published online 23 Dec). doi: 10.1016/S0140-6736(22)02597-1

3 Hentschke-Lopes M, Botton MR, Borges P, Freitas M, Mancuso ACB, Matte U. Sales of "COVID kit" drugs and adverse drug reactions reported by the Brazilian Health Regulatory Agency. *Cad Saude Publica* 2022;38:e00001022. doi: 10.1590/0102-311xen001022. pmid: 35894360

4 Mahase E. Covid-19: Budesonide shortens recovery time in patients not admitted to hospital, study finds. *BMJ* 2021;373:. https://www.bmj.com/content/373/bmj.n957. doi: 10.1136/bmj.n957 pmid: 33846115

5 Higgins AM, Berry LR, Lorenzi E, etalWriting Committee for the REMAP-CAP Investigators. Long-term (180-day) outcomes in critically ill patients with covid-19 in the Remap-Cap randomized clinical trial. *JAMA* 2023;329:-51. doi: 10.1001/jama.2022.23257. https://jamanetwork.com/journals/jama/fullarticle/2799870. pmid: 36525245