Bristol
lang.kathj26@gmail.com
Cite this as: *BMJ* 2023;383:p1612
http://dx.doi.org/10.1136/bmj.p1612
Published: 25 October 2023

COVID UNKNOWNS

What do we know about covid in immunocompromised people?

Katharine Lang looks at the continuing dangers of covid for immunocompromised people, the treatments available to them, and how antivirals such as remdesivir may help

Katharine Lang *freelance journalist*

Is covid still a particular risk for people who are immunocompromised?

Although the morbidity and mortality of covid-19 have reduced drastically in highly vaccinated and highly previously exposed populations, the disease is still a threat to the lives of more vulnerable people, particularly those without a functioning immune system. They are the people at "greatest risk," says Bill Schaffner, professor of preventive medicine and infectious diseases at Vanderbilt University in Nashville, Tennessee.

Around 12 000 people died of covid-19 worldwide from 1 to 28 May 2023, show data from the World Health Organization. Schaffner says that the patients who are dying are mainly immunocompromised people who are older—and therefore have weaker immune systems—or have underlying conditions such as cancer or an autoimmune disorder or are taking immunosuppressive drugs.

Alex Richter, professor in clinical immunology and director of the Clinical Immunology Service at the University of Birmingham, UK, reiterates this. "Studies are highlighting that although outcomes have improved for immune vulnerable patients, they remain at higher risk than the general population, and this is now included in risk algorithms such as QCovid,[1]" she says.

What we don't know is the difference in risk between different types of immunocompromised states. The evidence is not clear cut, says Arturo Casadevall, professor of molecular microbiology and immunology at Johns Hopkins Bloomberg School of Public Health in Baltimore, Maryland. "The data on [how at risk different immunocompromised people are] is fragmentary, since this group is very heterogeneous," he says. "For example, a patient on corticosteroids is very different from a transplant recipient, who in turn is very different from a person with leukaemia." Studies suggest that patients with malignancy or solid organ transplants are at greater risk of severe covid-19 and death.[2]

Immunocompromised people in general are also at risk of prolonged infection. "Some of these patients cannot clear infection once they get it, and that interferes with other therapies that they need," says Casadevall. "They remain PCR positive, often for months—a phenomenon called 'smouldering covid,' where the patients are chronically infected." These individuals pose a risk for the development of new variants and could theoretically serve as sources for new rounds of infection.[3]

How effective are SARS-CoV-2 vaccines in immunocompromised people?

About 2-3% of the general population have reduced immune responses, so they may be at greater risk from SARS-CoV-2 infection.[4] Regulatory and governmental bodies, including the US Centers for Disease Control and Prevention and the British Society for Immunology, therefore endorse covid vaccination for immunocompromised people on the grounds that the benefits outweigh the risks (since none of the covid vaccines are live, they're not thought to pose any more risk to this population than to immunocompetent people[5]). Trials in patients with HIV and those with solid organ transplants, although small in scale, have indicated that the Pfizer-BioNTech, Moderna, and Janssen vaccines are safe and effective in these groups.[5]

Vaccine shots may not be immediately effective, requiring boosters. Casadevall says that immunocompromised people may have a reaction that is "suboptimal since they have a compromised immune system, but [vaccination is] still recommended and some do respond after multiple shots."

Schaffner says, "There's a tendency for the antibodies that you've created to wane more rapidly [if you're an immunocompromised person] than when someone who has an intact and robust immune system receives vaccine. The current recommendation is: if you've received the bivalent booster you need wait only two months to get another." He adds that there seems to be no harm in repeatedly vaccinating immunocompromised individuals.

Close contacts of immunocompromised people are also urged to get vaccinated, but there's little evidence to support covid prophylaxis for either immunocompromised people or their contacts.[6] Richter emphasises how covid-19 has highlighted the risks among people with reduced immune response. "There was always a risk of infection for these individuals, which may not have been fully realised," she says. "There is a real need to support patients and help them understand their risk to allow them to make individual informed choices."

She reiterates the need for immunocompromised people to get their recommended vaccinations, to continue to wear masks, and to avoid situations that pose a high risk of infection, such as crowded or enclosed spaces.

What treatments are effective in immunocompromised patients?

Medicines to prevent the infection developing, clear the virus, or combat severe infection are vital for these patients. First line treatments have shown promise, such as the oral antivirals molnupiravir (Lagevrio) and nirmatrelvir-ritonavir (Paxlovid) and the injected antiviral remdesivir (Veklury).

One study found that molnupiravir might reduce the risk of severe covid-19 and death in elderly, female, and unvaccinated people.[7] Another found that, in a small group of immunocompromised patients, those who were treated with molnupiravir had a lower incidence of hospital admission and death than those who were not.[8] This was the first randomised controlled trial that showed molnupiravir's effectiveness, although the effect size was much lower than with nirmatrelvir-ritonavir or remdesivir. The UK Panoramic study later reported that molnupiravir showed no significant reductions in mortality or hospital admission in a vaccinated "high risk" population, although that trial involved few participants considered "highest risk" (severely immunosuppressed patients).[9] A review by the European Medicines Agency also questioned molnupiravir's effectiveness and recommended refusing marketing authorisation.[10]

Clinical trial results from nirmatrelvir-ritonavir in patients at risk of severe illness were impressive, showing an 89% reduction in hospital admission and death.[11] Real world results haven't been quite as striking, but one recent study found that the antiviral was effective in older and immunosuppressed patients.[12]

People who aren't given oral antivirals or for whom they're ineffective can still end up in hospital with severe covid-19. The treatment options then include intravenous antivirals such as remdesivir, and/or convalescent plasma.

What's the future of covid treatments for immunocompromised patients?

Oral versions of currently intravenous-only drugs such as remdesivir are in development, which would make them easier to access. Longer duration treatments are also needed, which could help reduce toxicity and lower the likelihood of drug resistance developing. Trials are already under way to study longer duration courses of nirmatrelvir-ritonavir—comparing the current five day course with 10 and 15 days—in immunocompromised adults.[13]

But as drug resistance is an ever growing worry, combination treatments seem a likely avenue for immediate exploration.[14] One small scale trial has found that a combination of remdesivir and nirmatrelvir-ritonavir with monoclonal antibodies induced a good clinical response in immunocompromised patients with prolonged or relapsed covid-19. Other trials suggest that combinations of convalescent plasma with different antivirals may be effective.[15]

Alternatives are needed, however, particularly where contraindications have severely limited the use of existing drugs. The ritonavir part of Paxlovid, for instance, works by preventing the liver from breaking down certain compounds, but this could be a major problem with other drugs a patient might need, as these also won't be broken down so might build to harmful levels.

Stephen Griffin, virologist at the University of Leeds, UK, says that ritonavir was part of the reason Paxlovid isn't licensed for under 18s. He explains, "There's such a huge raft of interactions between ritonavir and other drugs, because it acts on the liver to stop it degrading things. That is a real concern going forward for many clinically vulnerable people.

"For clinically vulnerable people on multiple medications, it's a bit of a minefield. Referring that out to GPs to manage may be a little difficult. They've got to work out, 'How does this interact with the meds my patient is on?'"

Is remdesivir still effective for treating covid-19?

Yes, but it faces questions over how effective it is and whether it's cost effective and practical as a standard treatment.

Originally developed to fight Ebola virus, the antiviral remdesivir was tested against SARS-CoV-2 at the height of the covid pandemic and was found to be effective as a covid treatment.

The catch is that remdesivir is administered intravenously. "The major issue is logistical," says Arturo Casadevall of Johns Hopkins University. "You need three infusions in three sequential days, and that can be very difficult for some patients, depending on their resources."

More commonly, doctors give it to hospital inpatients as a five or 10 day course. In non-ventilated patients with covid-19, remdesivir may shorten the time to recovery and reduce mortality.[16]

However, Alex Richter of the University of Birmingham highlights problems with availability. In the UK, she tells *The BMJ*, "access to remdesivir is very patchy and depends on individual hospital trusts and how they have chosen to interpret current NICE and government commissioning guidelines in the context of clinical unmet need." She adds that there's an urgent need to clarify current treatment options so that all clinically vulnerable patients can get access to treatments and clinical advice from clinicians with experience of treating covid infection in immune vulnerable people.

In immunocompromised patients remdesivir can suppress, but not always eradicate, SARS-CoV-2 when used over a longer period.[17] However, the problem with repeated or prolonged treatment with remdesivir is the possibility of viral resistance—something that concerns Stephen Griffin, a virologist at Leeds University. "The consequences of a pandemic virus becoming resistant, particularly for vulnerable people, could be really bad. There's no rescue therapy there," he tells *The BMJ*.

Efficacy and cost

Recent studies have also questioned the efficacy of remdesivir. One test of hospital inpatients[18] showed no evidence that it cleared the virus more quickly than if the drug hadn't been taken; another showed no benefit in patients severely ill with covid-19.[19] The suspicion is that the antiviral effects of remdesivir shown in the laboratory may not be replicated in patients.

Despite this, remdesivir does have advantages over some other covid treatments. Unlike Paxlovid, it can be used in under 18s, and few side effects or drug interactions have currently been reported. Oral versions of remdesivir are under investigation.[20]

Another major factor is cost. In the US remdesivir cost $520 (£397; €465) per 100 mg vial at the time of writing.[21] First treatment is two vials, then one vial daily until the end of the course, so a three day course totals over $2000, and the minimum hospital course of five days costs more than $3000. Added to the questions over its efficacy, this has led some experts to say that there's little justification for its use in hospital inpatients.

In the UK the latest recommendations from NICE state[22]: "Compared with standard care, remdesivir reduces death at day 28 in hospitalised people who require no or low-flow oxygen." However, "there is no evidence that remdesivir is more effective than placebo or standard care in treating hospitalised patients with covid-19 who require high-flow oxygen supplementation, non-invasive ventilation or invasive ventilation compared to standard care."

Competing interests: I have read and understood BMJ policy on declaration of interests and have no relevant interests to declare.

Provenance and peer review: Commissioned; externally peer reviewed.

1 Lyons J, Nafilyan V, Akbari A, etal. An external validation of the QCOVID3 risk prediction algorithm for risk of hospitalisation and death from COVID-19: An observational, prospective cohort study of 1.66m vaccinated adults in Wales, UK. *PLoS One* 2023;18:e0285979. doi: 10.1371/journal.pone.0285979. pmid: 37200350

2 Fung M, Babik JM. Covid-19 in immunocompromised hosts: what we know so far. *Clin Infect Dis* 2021;72:-50. doi: 10.1093/cid/ciaa863. pmid: 33501974

3 Hogan JI, Duerr R, Dimartino D, etal. Remdesivir resistance in transplant recipients with persistent coronavirus disease 2019. *Clin Infect Dis* 2023;76:-5. doi: 10.1093/cid/ciac769. pmid: 36156117

4 Shoham S, Batista C, Ben Amor Y, et al. Vaccines and therapeutics for immunocompromised patients with covid-19. *Lancet eClin Med* 2023. doi: 10.1016/j.eclinm.2023.101965

5 Duly K, Farraye FA, Bhat S. COVID-19 vaccine use in immunocompromised patients: A commentary on evidence and recommendations. *Am J Health Syst Pharm* 2022;79:-71. doi: 10.1093/ajhp/zxab344. pmid: 34455440

6 Bartoszko JJ, Siemieniuk RAC, Kum E, etal. Prophylaxis against covid-19: living systematic review and network meta-analysis. *BMJ* 2021;373:. doi: 10.1136/bmj.n949 pmid: 33903131

7 Najjar-Debbiny R, Gronich N, Weber G, etal. Effectiveness of molnupiravir in high-risk patients: a propensity score matched analysis. *Clin Infect Dis* 2023;76:-60. doi: 10.1093/cid/ciac781. pmid: 36130189

8 Johnson MG, Strizki JM, Brown ML, et al. Molnupiravir for the treatment of covid-19 in immunocompromised participants: efficacy, safety, and virology results from the phase 3 randomized, placebo-controlled MOVe-OUT trial. *Infection* 2023 (published online 17 Jan). doi: 10.1007/s15010-022-01959-9

9 Butler CC, Hobbs FDR, Gbinigie OA, etalPANORAMIC Trial Collaborative Group. Molnupiravir 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* 2023;401:-93. doi: 10.1016/S0140-6736(22)02597-1. doi: https://doi.org/10.1016/S0140-6736(22)02597-1

10 European Medicines Agency. Withdrawal of application for the marketing authorisation of Lagevrio (molnupiravir). 27 Jun 2023. https://www.ema.europa.eu/en/documents/medicine-qa/questions-answers-withdrawal-application-marketing-authorisation-lagevrio-molnupiravir_en.pdf

11 Mahase E. Covid-19: Pfizer's paxlovid is 89% effective in patients at risk of serious illness, company reports. *BMJ* 2021;375:. doi: 10.1136/bmj.n2713. pmid: 34750163

12 Najjar-Debbiny R, Gronich N, Weber G, etal. Effectiveness of paxlovid in reducing severe coronavirus disease 2019 and mortality in high-risk patients[Erratum in: *Clin Infect Dis* 2023;76:-9]. *Clin Infect Dis* 2023;76:-9. doi: 10.1093/cid/ciac443. pmid: 35653428

13 Mikulska M, Sepulcri C, Dentone C, etalTriple combination therapy with 2 antivirals and monoclonal antibodies for persistent or relapsed severe acute respiratory syndrome coronavirus 2 infection in immunocompromised patients. *Clin Infect Dis* 2023;. doi: 10.1093/cid/ciad181

14 Looi M-K. What is the future for covid drugs and treatments?*BMJ* 2023;381:. https://www.bmj.com/content/381/bmj.p1001. doi: 10.1136/bmj.p1001 pmid: 37164386

15 Bloch EM, Focosi D, Shoham S, etal. Guidance on the use of convalescent plasma to treat immunocompromised patients with coronavirus disease 2019. *Clin Infect Dis* 2023;76:-24. doi: 10.1093/cid/ciad066. pmid: 36740590

16 Gottlieb RL, Vaca CE, Paredes R, etalGS-US-540-9012 (PINETREE) Investigators. GS-US-540-9012 (PINETREE) Investigators. Early remdesivir to prevent progression to severe covid-19 in outpatients. *N Engl J Med* 2022;386:-15. doi: 10.1056/NEJMoa2116846. pmid: 34937145

17 Helleberg M, Niemann CU, Moestrup KS, etal. Persistent covid-19 in an immunocompromised patient temporarily responsive to two courses of remdesivir therapy. *J Infect Dis* 2020;222:-7. doi: 10.1093/infdis/jiaa446. pmid: 32702095

18 Krifors A, Karlsson L, Ekman M, et al. The kinetics of SARS-CoV-2 viremia in covid-19 patients receiving remdesivir. *Eur J Clin Microbiol Infect Dis* 2023 (published online 27 May). doi: 10.1007/s10096-023-04627-4

19 Garibaldi BT, Wang K, Robinson ML, etal. Real-world effectiveness of remdesivir in adults hospitalized with coronavirus disease 2019 (covid-19): a retrospective, multicenter comparative effectiveness study. *Clin Infect Dis* 2022;75:-24. doi: 10.1093/cid/ciab1035 pmid: 34910128

20 Cao Z, Gao W, Bao H, etal. VV116 versus nirmatrelvir-ritonavir for oral treatment of covid-19. *N Engl J Med* 2023;388:-17. doi: 10.1056/NEJMoa2208822. https://www.nejm.org/doi/full/10.1056/nejmoa2208822. pmid: 36577095

21 Whittington MD, Pearson SD, Rind DM, Campbell JD. The cost-effectiveness of remdesivir for hospitalized patients with covid-19. *Value Health* 2022;25:-50. doi: 10.1016/j.jval.2021.11.1378. pmid: 35190252

22 National Institute for Health and Care Excellence. Covid-19 rapid guideline: Managing covid-19 (v 29.2). 11 Jul 2023. https://www.nice.org.uk/guidance/ng191/resources/covid19-rapid-guideline-managing-covid19-pdf-51035553326