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.

Elsevier must end its fossil fuel partnerships and subsidies

Elsevier, *The Lancet*'s publisher, continues to subsidise climate pollution through analytic tools and new journals supporting coal, oil, and gas exploration and extraction—an ongoing partnership that is morally and materially insupportable.

Richard Horton calls climate change the most important existential crisis facing the human species,[1] supported by the unjust burden of mortality and morbidity catalogued in the *Lancet* Countdown on health and climate change. For human safety, most known oil and gas, and almost all coal, must remain in the ground. Further, the Intergovernmental Panel on Climate Change (IPCC) now identifies unethical lobbying by coal, oil, and gas industries as the major barrier to climate action.

On behalf of Climate Health Aotearoa, a national climate change and health research centre in New Zealand, we call on *The Lancet*'s Editorial Board to demand an end to Elsevier's support for fossil fuel industries. We urge The Lancet Group to ensure Elsevier upholds the Group's ethical commitment: that the best science must lead to better lives.

We declare no competing interests.

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Publisher's reply

As a scientific publisher and information analytics company, we take our responsibility seriously. We have been supporting sustainability research and working to reduce our environmental impact for more than 15 years. In 2021, we made a firm pledge to become net zero for all direct and indirect emissions by 2040.

We support the advancement of knowledge about climate change and its impacts through the research that we publish and analytical tools that deliver insights for evidence-based policy, innovation, and action. In 2021, we published *Pathways To Net Zero: the impact of clean energy research*, a report that we followed up in 2022, ahead of COP27, with *Pathways To Net Zero: global south research in the transition to clean energy* to analyse the role of clean energy research in the global south.

We have accelerated the transition of our products to focus on renewable energy. Only six of our 2800 journals currently relate to hydrocarbon science, with updated aims and scope to focus on topics such as renewable energy, and carbon capture and storage. We are working to ensure our editorial boards have the right expertise and balanced representation. Our Elsevier Energy Books Teams have adopted Energy With Purpose as their mission, which is a commitment to only commission content that supports and advances the energy transition and the reduction of CO_2 emissions.

At Elsevier, we hold ourselves accountable to take climate action and deliver on our net zero pledge. We have made solid progress but know that there is more to do. We will continue to collaborate with the communities we serve and share our progress and learnings, and we welcome feedback from all stakeholders.

I am Executive Vice President of Elsevier Global Communications.

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WHO's Therapeutics and COVID-19 Living Guideline on mAbs needs to be reassessed

An essential line of defence in a global living-with-COVID-19 policy is formed by effective therapeutic strategies for vulnerable patients,[1] many of whom are excluded from treatment with nirmatrelvir–ritonavir (sold as Paxlovid, Pfizer) by virtue of their comorbidities or interacting medications. Preliminary data suggest that monoclonal antibodies (mAbs) are highly effective for these groups,[2] and WHO, in its Therapeutics and COVID-19: Living Guideline,[3] has previously conditionally recommended the use of sotrovimab (sold as Xevudy, Vir Biotechnology and GlaxoSmithKline) or casirivimab–imdevimab (sold as Ronapreve, Regeneron) for people at high risk of hospitalisation. However, in a Sept 16, 2022, update,[4] WHO issued a "strong recommendation against" use of these mAbs, stating that they "[do] not neutralize the currently circulating variants of SARS-CoV-2 and their subvariants".[4]

This guidance requires an urgent reassessment. Based on analysis of both the existing literature and data presented here, mAbs neutralise circulating variants and remain the best treatment option for many vulnerable patients, offering a high benefit-to-risk ratio.

To measure neutralising capabilities of mAbs, we used live-virus microneutralisation assays on Good Clinical Practice-compliant high-throughput platform,[5–7] calibrated to WHO International Standards[8,9] for anti-SARS-CoV-2 immunoglobulin (WHO/BS/2020.2403 and WHO/BS/2022.2427, which we contributed to the calibration of) against sequence-validated batches of nine SARS-CoV-2 variants. Further methodological details on mAbs, virus variants and culture, high-throughput live virus microneutralisation assays, and data analysis, statistics, and availability are available in the appendix.

This work was a benchmarking exercise between the Crick COVID Surveillance Unit and the Legacy study, an ongoing collaboration between University College London Hospitals and the Francis Crick Institute in

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For **The Lancet Group's pledge** see https://www.thelancet.com/about-us

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See **Online** for appendix

London, UK. Legacy was approved by the London Camden and Kings Cross Health Research Authority Research and Ethics committee (IRAS number 286469) and is sponsored by University College London.

We assayed a panel of mAbs: sotrovimab; casivirimab and imdevimab (sold as Ronapreve, Regeneron); and tixagevimab and cilgavimab (sold as Evusheld, AstraZeneca). EC_{50} values were calculated by fitting a four-parameter dose–response curve to 288 independent data points, generated from three independent repeats of 12 independent titrations, each consisting of two technical replicates of a four-point dilution series against live SARS-CoV-2 variants (appendix p 2). This approach enabled refined determination of EC_{50} values and corresponding 95% CIs (appendix pp 3–4). We found that sotrovimab, imdevimab, and cilgavimab neutralised omicron BA.2, BA.2.12.1, BA.4, and BA.5.

Many reports focus their narrative and data presentation on the reduction of neutralisation of a given mAb relative to ancestral SARS-CoV-2; however, this metric is less helpful in assessing efficacy since starting absolute titres versus ancestral virus vary widely, and mAbs formulation, dosing, and administration also vary. Similarly, in the absence of real-world efficacy data, consideration of the EC_{50} value relative to pharmacokinetic data (eg, measured serum concentrations of mAbs post-administration) requires assumptions regarding tissue penetration and mechanism of action.

In this context, technical aspects of neutralisation assays matter: many laboratories continue to use ACE2-overexpressing cells, despite such cells showing an aberrant lack of neutralisation of SARS-CoV-2 by certain classes of mAbs (including sotrovimab[10]) and at a fundamental level, comparison across laboratories is hampered by the use of different cell lines that may be infected by SARS-CoV-2 variants to different extents. Here, calibration with the WHO International Standard for anti-SARS-CoV-2 immunoglobulin and reporting of neutralisation titres in International Units (appendix p 5) would be useful to facilitate such comparisons. Additionally, reporting of CIs (rather than point estimates) is essential to evaluate the significance of any possible changes in neutralisation—especially when considering EC_{90} values, which lie close to the plateau of the dose–response curve and are inherently noisy, both in cell-based assays and in fitting of a dose–response curve.

With the emergence of the omicron BA.2 subvariant in early 2022, the US Food and Drug Administration (FDA) found a decrease in microneutralisation titre EC_{90} of 25–48-fold relative to ancestral SARS-CoV-2.[11] On April 5, 2022, the FDA withdrew approval of sotrovimab[12] on the basis of their assay results and pharmacokinetic modelling suggesting that the authorised dose was unlikely to be effective against BA.2. In wider reporting, including medical literature,[13] the prevailing (but, in our view, erroneous) view became that sotrovimab is ineffective against BA.2 and BA.5, with the dose aspect of the FDA's statement set aside.

We found that sotrovimab neutralised BA.2 with an EC_{50} of 1849 ng/mL (95% CI 1429–2391), representing a 22-fold reduction versus ancestral SARS-CoV-2, with the EC_{50} remaining 64-fold below the mean peak serum concentration of sotrovimab (appendix p 6) and 13-fold below the mean serum concentration 28 days post-administration. These and other data led UK health authorities, in contrast to US health authorities, to retain sotrovimab for the treatment of extremely clinically vulnerable patients who are at risk of progression to severe COVID-19, given the absence of an alternative approved mAb and clinical data showing a reduction in real-world efficacy.

It remains challenging to integrate clinical trial results into these assessments. Most trials use a primary endpoint of a positive COVID-19 test since they recruit too few participants to power the statistical analysis of progression to severe disease, which would be the more relevant metric for clinical practice for extremely clinically vulnerable patients and for public health policy to reduce the burden on health-care infrastructure. However, large-scale analyses of digital primary care health records from the UK National Health Service, linking clinical outcomes with patient metadata, have recently shown that sotrovimab was superior to treatment with molnupiravir in preventing COVID-19-related hospitalisation and death in extremely clinically vulnerable populations during the period of the omicron BA.2 wave.[2]

This demonstration of sotrovimab's efficacy against BA.2 can be used in conjunction with our in-vitro neutralisation data to conservatively infer real-world efficacy against emerging variants of concern: those that are neutralised to the same extent as, or even better than, BA.2 (numerically, a lower EC_{50}) would be expected to remain effective. We found that sotrovimab neutralised BA.4, BA.5, and BA.2 to similar extents (EC_{50}=1490 ng/mL; 95% CI 881–2517), suggesting that sotrovimab would remain effective against BA.5. Similarly, a second-generation BA.2 variant, BA.2.12.1, was neutralised to a greater extent than parental BA.2 (EC_{50}=1211 ng/mL; 95% CI 844–1738), in line with preliminary pseudotyped lentivirus neutralisation data on a wider set of second-generation omicron sublineages, including BA.2.75.2.[14] In light of this evidence, it would be reasonable to retain the use of sotrovimab, especially in extremely clinically vulnerable patients who test positive for COVID-19 and have few other options.

The lack of directionality in the degree of neutralisation by a mAb and successive variants is worth highlighting, perhaps most strikingly in the case of the imdevimab component of Ronapreve. As omicron spread in the

UK in December, 2021, we and others found that BA.1 fully escaped from casirivimab–imdevimab in vitro,[7,15–17] with no neutralisation whatsoever at concentrations up to 18 750 ng/mL. UK policy was then changed to restrict the usage of casirivimab–imdevimab to infection with a non-omicron variant on Dec 24, 2021, during the UK's transition from delta to omicron BA.1.[18] However, we later found that the imdevimab component of Ronapreve was able to neutralise subsequent omicron BA.2, BA.2.12.2, BA.4, and BA.5 variants (appendix p 4). For BA.4 and BA.5, this value is 536-fold below the mean peak serum concentration and 92-fold below the mean serum concentration 28 days post-administration (appendix p 6), reflecting a greater degree of neutralisation by imdevimab than sotrovimab in vitro, despite only the latter remaining in clinical use.

Our results on imdevimab are consistent with other reports published in June–August, 2022.[19–21] All together, the evidence does not support WHO's decision in September, 2022, to withdraw conditional recommendation of casirivimab–imdevimab for seronaive patients. Regulators might need to re-evaluate withdrawn mAbs in light of evidence of regained activity against the spike protein of a future variant.

In the case of sotrovimab, the combined evidence from our in-vitro neutralisation and real-world clinical efficacy data supports its continued use against circulating omicron variants, including BA.4 and BA.5. The ongoing evolution of SARS-CoV-2 variants and continued global transmission has resulted in a situation where new variants can replace one another within weeks. Although WHO's Living Guideline[4] posits the "need for clinical trial evidence in order to confirm any clinical effectiveness of new monoclonal antibodies that reliably neutralize the circulating strains", generating this evidence is challenging since the results would almost instantly become obsolete. This situation is compounded by the overall low rate of hospital admissions in the face of high levels of population immunity: trialists struggle to recruit sufficient participants to power analysis of efficacy of new therapies against progression to severe illness.

Overall, our results highlight how the regulatory environment for mAbs has not kept pace—a fact also illustrated by the cilgavimab component of Evusheld, which showed strong neutralisation against all omicron variants tested here (appendix p 4). Evusheld is now approved for treatment in Europe and Japan but remains approved only for prophylactic use in the USA and the UK, in part due to a dogmatic focus by some regulators on not licensing the same therapeutics for prophylaxis and treatment of acute COVID-19. Bebtelovimab (not studied here and not assessed in WHO's Living Guideline[4]) remains unavailable outside the USA,[22,23] where the FDA adopted a more relaxed approach to Emergency Use Authorisation based on data showing improved symptoms and somewhat reduced viral loads from phase 1 and 2 trials together with in-vitro neutralisation data.[24] That regulatory flexibility is limited: although long experience with antiviral therapies suggests mAb combination therapy (eg, across mAb classes or in combination with small-molecule antivirals) is preferrable to monotherapy, the regulatory and commercial backdrop makes these kinds of cross-company trials challenging. The net result is that effective monoclonals are available but not offered to extremely clinically vulnerable patients with COVID-19 who are at risk of progressing to severe disease.

We recommend, first, that WHO's Living Guideline[4] be further updated to reflect the available data, and second, that more responsive regulatory approaches are developed to integrate high-quality, standardised live-virus neutralisation data with efficacy data from real-world clinical use. This approach might contribute positively towards determining an index of protection for a given mAb (or class of mAbs with shared Fc modifications considered as a single platform)—analogous to a correlate of protection for vaccine-induced antibodies.

At present there is an unrealistically high threshold to enter a therapeutic agent into clinical practice. The threshold to withhold or withdraw the same agent is much lower when based on in-vitro evidence for loss of potency alone. Such a situation disproportionately affects vulnerable patients whose other essential medications or comorbidities exclude COVID-19 therapeutics other than a neutralising mAb. This situation also strongly disincentivises development of novel antivirals that are needed to continue to offer protection to highly vulnerable populations.

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For **data and full R code** see https://github.com/davidlvb/Crick-UCLH-Legacy-Monoclonals-2022-10

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For the **Therapeutics and COVID-19 Living Guidelines** see https://app.magicapp.org/#/guideline/6672

WHO Living Guidelines on antivirals for COVID-19 are evidence-based

Mary Wu and colleagues[1] suggest a change to WHO's COVID-19 treatment guidelines for monoclonal antibodies. These Living Guidelines were updated on Sept 16, 2022, with strong recommendations against the use of sotrovimab and casirivimab–imdevimab following the emergence of new SARS-CoV-2 variants and subvariants.[2] We, as members of the WHO panel responsible for presenting the evidence to the Guideline Development Group (GDG), welcome this opportunity to elaborate on the evidence considered during the GDG meeting.

Wu and colleagues present in-vitro data that provide further evidence that neutralisation is equivalent for sotrovimab between BA.2, BA.4, and BA.5 omicron lineages. Their findings support interpretation of the data considered[3–5] during development of the guideline[2] that led the GDG to conclude similar reduction in neutralisation between these sublineages. However, Wu and colleagues present an over-simplistic assessment of the neutralisation data in the context of the compartmental pharmacokinetics of monoclonal antibodies. As a result, Wu and colleagues make incorrect inferences regarding the interpretation of the in-vitro neutralisation data in the context of clinical effectiveness. When appropriately assessed, the new data does not change the basis on which the original decision to recommend against sotrovimab was made. Although neutralisation of these lineages via sotrovimab appears equivalent and lower than previous variants, it is also insufficient to confer the clinical effectiveness of sotrovimab reported in the pre-omicron era.

The analysis presented to the GDG during their deliberations included arguments presented by the US Food and Drug Administration for the use of sotrovimab—arguments that Wu and colleagues neither acknowledged nor rebutted.[6] Specifically, this analysis included two aspects. First, as per antiviral pharmacology convention, when serum concentrations are corrected for penetration into the lung, the target concentrations (defined by the effective concentration required for 90% neutralisation [EC_{90}] of BA.2 omicron) are unlikely to be achieved. Second, applying an EC_{90} fold-change