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 hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Correspondence

November 10, 2022

For the Therapeutics and COVID-19 Living Guidelines see https://app.mappycorp.org/ni/ guideline/6672

2196

The Correspondence Section is intended for presentation of new or novel data, or particularly important comments on published material, and is not intended for discussion of reviews and other standard articles. Correspondence will normally be published in English and the decision to accept for publication is made by the Editor. Each Correspondence should be accompanied by a brief summary and should not exceed 1400 words, including references. There is a limit of five authors for each Correspondence.

Mary Wu and colleagues suggest a change to WHO's COVID-19 therapeutics for monoclonal antibodies. These Living Guidelines were updated on Sept 16, 2022, with strong recommendations against the use of sotrovimab and casirivimab-idevirmab following the emergence of new SARS-CoV-2 variants and subvariants. 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 monoclonal lineages. Their findings support interpretation of the data considered during development of the guideline 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. 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 [EC90] of BA.2) of BA.2 omicron) are unlikely to be achieved. Second, applying an \( EC_{50} \) fold-change

1. UK Government Cabinet Office. COVID-19 response: living with COVID-19. May 6, 2022. https://www.gov.uk/government/publications/covid-19-response-living-with-covid-19-covid-19-response-living-with-covid-19 (accessed May 6, 2022).
2. Zheng B, Green ACA, Tazerj, et al. Comparative effectiveness of sotrovimab and molnupiravir for prevention of severe COVID-19 outcomes in non-hospitalised patients: an observational cohort study using the OpenSAFELY platform. bioRxiv 2022; published online Sept 22. https://doi.org/10.10111/2022.05.22.2275417 (preprint).
3. WHO. Therapeutics and COVID-19: living guideline. July 14, 2022. https://apps.who.int/iris/bitstream/handle/10665/359774/WHO-2019-nCoV-therapeutics-2022.4-eng.pdf (accessed Sept 21, 2022).
4. WHO. Therapies and COVID-19: living guideline. Sept 16, 2022. https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2022.5 (accessed Sept 21, 2022).
5. Wall EC, Wu M, Harvey R, et al. Neutralising antibody activity against SARS-CoV-2 VOCs B.1.617.2 and B.1.617.3. Lancet 2021; 397:2331-33.
6. Wall EC, Wu M, Harvey R, et al. AAZ222-induced neutralising antibody activity against SARS-CoV-2 Delta VOC. Lancet 2022; 398:207-09.
7. Wu M, Wall EC, Carr EJ, et al. Three-dose vaccination elicits neutralising antibodies against omicron. Lancet 2022; 399:75-77.
8. Mattsson G, Bentley EM, Hassall M, et al. WHO/BS/2020.2403 Establishment of the WHO International Standard and Reference Panel for anti-SARS-CoV-2 antibody. Nov 18, 2020. https://www.who.int/publications/m/item/WHO-BS/2020-2403 (accessed July 13, 2022).
9. Bentley EM, Atkinson E, Rigby P, et al. WHO/BS/2022.2427 Establishment of the 2nd WHO International Standard for anti-SARS-CoV-2 immunoglobulin and Reference Panel for antibodies to SARS-CoV-2 variants of concern. July 19, 2022. https://www.who.int/publications/m/item/who-bs-2022-2427 (accessed Sept 21, 2022).
10. Lempp FA, Soriaga LB, Montiel-Ruiz M, et al. Lectors enhance SARS-CoV-2 infection and influence neutralising antibodies. Nature 2021; 598:342-47.
11. US Food and Drug Administration. Fact sheet for healthcare providers Emergency Use Authorization (EUA) of sotrovimab authorized use. March, 2022. https://www.fda.gov/media/149534/download (accessed May 6, 2022).
12. US Food and Drug Administration. FDA updates sotrovimab emergency use authorization. April 5, 2022. https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-sotrovimab-emergency-use-authorization (accessed May 6, 2022).
13. Mahase E. Covid-19: has the spread of omicron BA.2 made antibody treatments redundant? BMJ 2022; 377:e01009.

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

Mary Wu and colleagues 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-idevirmab following the emergence of new SARS-CoV-2 variants and subvariants. 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 monoclonal lineages. Their findings support interpretation of the data considered during development of the guideline 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. 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 [EC90] of BA.2) of BA.2 omicron) are unlikely to be achieved. Second, applying an \( EC_{50} \) fold-change
in neutralisation activity between BA.2 omicron and delta (B.1.617.2) variants, the serum neutralisation titres were likely to be less than the serum neutralisation titres among participants allocated to the 250 mg intramuscular group of the COMET-TAIL randomised controlled trial (RCT). This 250 mg intramuscular group had a higher rate of hospitalisation than the 500 mg group (intramuscular or intravenous), and, therefore, this arm of the trial was terminated early. Presented with this evidence, the GDG unanimously agreed that the clinical effectiveness of sotrovimab against BA.2 omicron was highly uncertain. The GDG also reviewed the available in-vitro neutralisation data for BA.4 and BA.5 omicron\(^3 \text{–} 5\) and concluded that similar reductions in neutralisation existed.

The in-vitro neutralisation data presented by Wu and colleagues do not alter the interpretation of the original in-vitro data for several reasons. First, \(EC_{90}\), the concentration required to neutralise 50% of the virus population, would allow the remaining 50% of the virus population to be able to replicate. Antiviral pharmacology convention, as applied by regulatory agencies and the companies developing monoclonal antibodies, dictates that \(EC_{90}\) represents most of the viral population being neutralised and is the appropriate parameter when defining the threshold. \(EC_{90}\) is at least nine times higher than \(EC_{50}\).

Second, not fully neutralising the virus population not only carries the risk of inefficacy but also increases the likelihood of emergence of selected resistance. Emergence of selected resistance has already been widely documented with sotrovimab use against susceptible variants, particularly in the context of immunocompromised patients.\(^6 \text{–} 12\) The WHO panel acknowledges that the calculation of \(EC_{90}\) is less precise than the calculation of \(EC_{50}\), but does not accept that this imprecision in measurement is a valid rationale for using a suboptimal threshold.

Third, systemic circulation is not the predominant target compartment for replication of SARS-CoV-2, and antiviral medicines must penetrate tissues, particularly those of the respiratory tract. Wu and colleagues correctly assert that the true penetration of sotrovimab into the relevant target compartment (often assumed to be the lung) is unknown. However, not knowing the degree of penetration into the correct compartment does not constitute a legitimate basis to ignore the need for penetration to achieve clinical effectiveness. On the basis of available empirical and quantitative pharmacology evidence for other monoclonal antibodies,\(^13 \text{–} 17\) national agencies proposed a lung-to-serum ratio of 6·5–12·0%. The WHO panel supports this view.

Fourth, Wu and colleagues assert that since the peak serum concentrations exceed the sotrovimab BA.2 \(EC_{90}\) by 64-fold at maximum \((C_{\text{max}})\) and by 13-fold at day 28 post-administration, continued use of sotrovimab should be recommended.\(^1\) However, this ignores the issue of penetration into the lung and the necessary \(EC_{90}\) threshold. Applying their own in-vitro neutralisation data and the most lenient appropriate analysis (12% lung penetration with an \(EC_{90}\)), the serum concentration is not expected to achieve the BA.2 tissue-adjusted \(EC_{90}\) concentration at \(C_{\text{max}}\) (by a ratio of 0·85) or at day 28 (ratio 0·18). Conversely, the new data highlight that for the pre-omicron variants studied in RCTs, the serum concentrations exceeded the tissue-adjusted \(EC_{90}\) at \(C_{\text{max}}\) (ratio 19·0 for ancestral SARS-CoV-2) and at day 28 (ratio 4·0 for ancestral SARS-CoV-2).

Finally, the evaluation of serum neutralisation titres in the COMET-TAIL trial is not addressed by Wu and colleagues.\(^1\) This analysis\(^5\) leverages data from an RCT and assesses the serum concentration and \(EC_{90}\) independent of the uncertainties regarding tissue penetration. When this analysis is repeated using a 22-fold-reduction in activity for BA.2, BA.4, and BA.5 omicron relative to ancestral SARS-CoV-2 (as asserted by Wu and colleagues,\(^1\) but which might under-represent the actual reduction in \(EC_{90}\)), the serum neutralisation titres would be expected to remain less than the neutralisation titres detected within the 250 mg intramuscular arm of COMET-TAIL. Thus, ineffectiveness would be anticipated at this level. Moreover, the COMET-TAIL trial was conducted while the delta variant was most prevalent in the US population, and the difference in \(EC_{90}\) between the BA.2 omicron variant and the delta variant was 51·4-fold according to Wu and colleagues.\(^1\)

Considered together, the in-vitro neutralisation data presented by Wu and colleagues\(^1\) do not materially change the interpretation of the analysis considered by the GDG, but they do provide additional evidence that the evaluation of BA.2 omicron neutralisation by sotrovimab is also applicable to BA.4 and BA.5 omicron.

Wu and colleagues\(^1\) apply the same reasoning to other monoclonal antibodies. For imdevimab, no RCT data are available for doses that were discontinued due to reduced efficacy against any SARS-CoV-2 variant and so an analogous serum neutralisation analysis is not possible. However, using neutralisation data presented by Wu and colleagues,\(^1\) it is possible to ascertain (using \(EC_{90}\) as a best-case scenario) a 93·3-fold reduction in neutralisation compared with ancestral SARS-CoV-2 of BA.2 omicron, and a 37·6-fold reduction in neutralisation compared with ancestral SARS-CoV-2 of both BA.4 and BA.5 omicron by imdevimab. Casirivimab has no neutralisation activity against any omicron sub-lineage. RCTs were conducted using casirivimab–imdevimab combination, and no RCT data are currently available for imdevimab as a monotherapy. Regarding tixagevimab–cilgavimab combination, the WHO panel finds that available data are insufficient to make...
any recommendation for treatment, that tixagevimab does not neutralise BA.4 and BA.5 omicron, and that emerging data suggest that several circulating subvariants (including BA.4,6, BA.2.75.2, BQ.1, BQ.1.1, and XBB) are not neutralised by tixagevimab or cilgavimab.

Wu and colleagues also cite exploratory analyses that were included within a preprint describing a retrospective observational cohort from the UK as a basis for concluding continued efficacy of sotrovimab for BA.2 omicron. The biases of observational studies are well established, which is why the GDG insists on evidence derived from RCTs to support recommendations for pharmaceutical agents or antibodies. Although in-vitro evidence suggests absence of clinical effectiveness, data from clinical trials remain necessary to prove effectiveness.

The body of evidence regarding the clinical effectiveness of COVID-19 therapeutics is growing rapidly, but unfortunately not as rapidly as the occurrence of new variants. Therefore, trustworthy living guidelines, created by panels free of competing interests, need to continuously interpret clinical effectiveness beyond initial authorisation from regulatory agencies. The choice of therapeutic options is often most limited for highly vulnerable patients, but an over-optimistic inference regarding the clinical effectiveness of a given agent inevitably comes with burden, cost, and adverse effect, and will not serve the interests of individual patients or health systems.

AO is a director of Tandum Nano and co-inventor of drug delivery patents unrelated to medicines discussed in this Correspondence. AO has been co-investigator on funding received by the University of Liverpool from VIIV Healthcare and Gilead Sciences unrelated to COVID-19 in the past 3 years. AO has received personal fees from Gilead and Assembly Biosciences in the past 3 years unrelated to COVID-19 research. AO is a member of the Trial Management Group for the AGILE phase 1/2 platform trial and AGILE has received funding from Ridgeback and GlaxoSmithKline in the past 3 years for which AO was not a co-investigator. These disclosures were reviewed by WHO before discussions with the GDG, which deemed them not to present a conflict of interest. All other authors declare no competing interests.

*Andrew Owen, Janet Victoria Diaz, Gordon Guyatt, François Lamontagne, Miriam Stegeman, Per Olav Vandvik, Thomas Agoritsas aowen@liverpool.ac.uk

Centre of Excellence in Long-acting Therapeutics, Department of Pharmacology and Therapeutics, Materials Innovation Factory, University of Liverpool, Liverpool L7 8YN, UK (AO); World Health Organization, Geneva, Switzerland (JVD); Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, ON, Canada (GG); Department of Medicine, Université de Sherbrooke, Sherbrooke, QC, Canada (FL); Department of Infectious Diseases and Respiratory Medicine Berlin, Charité-Universitätsmedizin Berlin, Germany (MS); MAGIC Evidence Ecosystem Foundation, Oslo, Norway (POV); Department of Medicine, University Hospitals of Geneva, Geneva, Switzerland (TA)

1 Wu MY, Carr EJ, Harvey R, et al. WHO’s Therapeutics and COVID-19 Living Guideline on mAbs needs to be reassessed. Lancet 2022; published online Oct 9. https://doi.org/10.1016/S0140-6736(22)03198-9
2 Agarwal A, Rochwerger B, Lamontagne F, et al. A living WHO guideline on drugs for COVID-19. BMJ 2020; 370: m3379.
3 Arora P, Kempf A, Nehmeier I, et al. Augmented neutralisation resistance of emerging omicron subvariants BA.2.1.2.1, BA.4, and BA.5. Lancet Infect Dis 2022; 22: 1117–18.
4 Cao Y, Iyomami A, Jian F, et al. BA.2.1.2.1, BA.4, and BA.5 escape antibodies elicited by omicron infection. Nature 2022; 608: 593–602.
5 Yamashita D, Kosuga Y, Kimura J, et al. Neutralisation sensitivity of SARS-CoV-2 omicron subvariants to therapeutic monoclonal antibodies. Lancet Infect Dis 2022; 22: 942–43.
6 US Food and Drug Administration. Emergency use authorization (EUA) for sotrovimab Center for Drug Evaluation and Research (CDER) memorandum. March 25, 2022. https://www.fda.gov/media/175755/download (accessed Oct 13, 2022).
7 Rockett R, Basile K, Maddocks S, et al. Resistance mutations in SARS-CoV-2 delta variant after sotrovimab use. N Engl J Med 2022; 386: 1477–79.
8 Gliha S, Luebeck N, Killer A, et al. Rapid selection of sotrovimab escape variants in SARS-CoV-2 omicron infected immunocompromised patients. Clin Infect Dis 2022; published online Oct 3. https://doi.org/10.1093/cid/ciac802.
9 Andrés C, González-Sánchez A, Jiménez M, et al. Emergence of delta and omicron variants carrying resistance-associated mutations in immunocompromised patients undergoing sotrovimab treatment with long-term viral excretion. Clin Microbiol Infect 2022; published online Sept 5. https://doi.org/10.1016/j.cmi.2022.08.021.