THE LANCET

Supplementary appendix

This appendix formed part of the original submission. We post it as supplied by the authors.

Supplement to: 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 6. https://doi.org/10.1016/S0140-6736(22)01938-9.

Appendix for

Clinical and *in vitro* evidence support reassessment of WHO Living Guideline on monoclonal antibody therapy for COVID-19

Mary Y Wu[1], Edward J Carr[1], Ruth Harvey[2], Harriet V Mears[1], Svend Kjaer[1], Hermaleigh Townsley[1,2], Agnieszka Hobbs[1], Martina Ragno[1], Lou S Herman[1], Lorin Adams[2], Steve Gamblin[1], Michael Howell[1], Rupert Beale[1], Michael Brown[3], Bryan Williams [3,4], Sonia Gandhi[1,4], Charles Swanton[1,4], Emma C Wall[1,3], and David LV Bauer[1,5]

Affiliations

1. The Francis Crick Institute, 1 Midland Road, London, UK
2. Worldwide Influenza Centre, The Francis Crick Institute, 1 Midland Road, London, UK
3. National Institute for Health Research (NIHR) University College London Hospitals (UCLH) Biomedical Research Centre and NIHR UCLH Clinical Research Facility, London, UK
4. University College London, Gower Street, London
5. Genotype-to-Phenotype UK National Virology Consortium (G2P-UK)

Correspondence to:
David LV Bauer david.bauer@crick.ac.uk

Contents

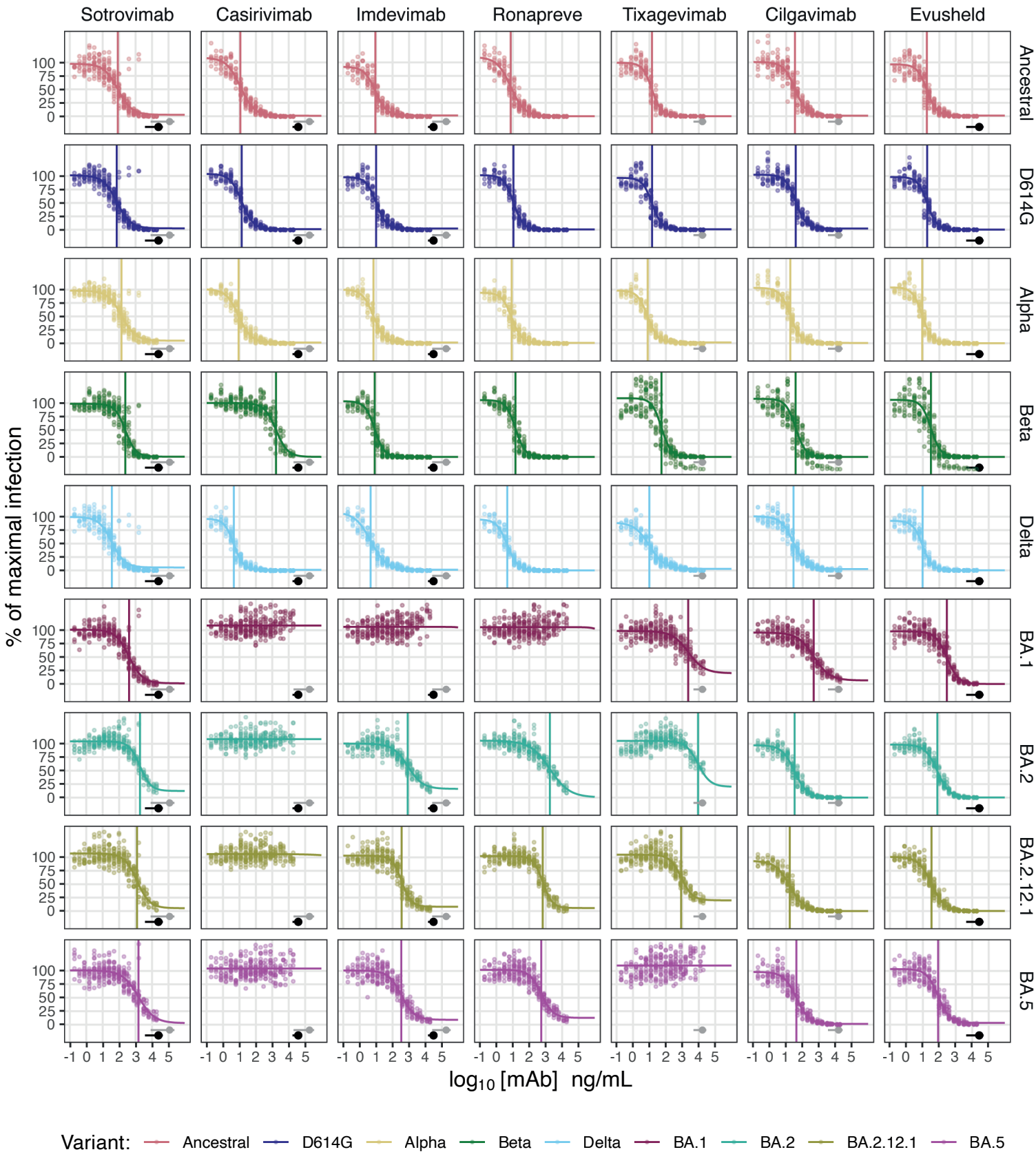

Figure 1. Neutralisation of SARS-CoV-2 variants by monoclonal antibodies (mAbs). For each combination of mAb and SARS-CoV-2 variant, 288 independent data points are shown, which were generated from 3 independent repeats of 12 independent titrations, each consisting of 2 technical replicates of a 4-point dilution series against live SARS-CoV-2 virus. EC_{50} values (solid vertical lines) by were calculated fitting a 4-parameter dose-response curve (solid curves) to this data. For each mAb, the mean serum concentration at maximum (grey point) and twice its standard deviation (grey error line), and at 28 days post-administration (black points) and twice its standard deviation (black error line) was obtained from its Summary of Product Characteristics (see Table 3) and plotted here for reference.

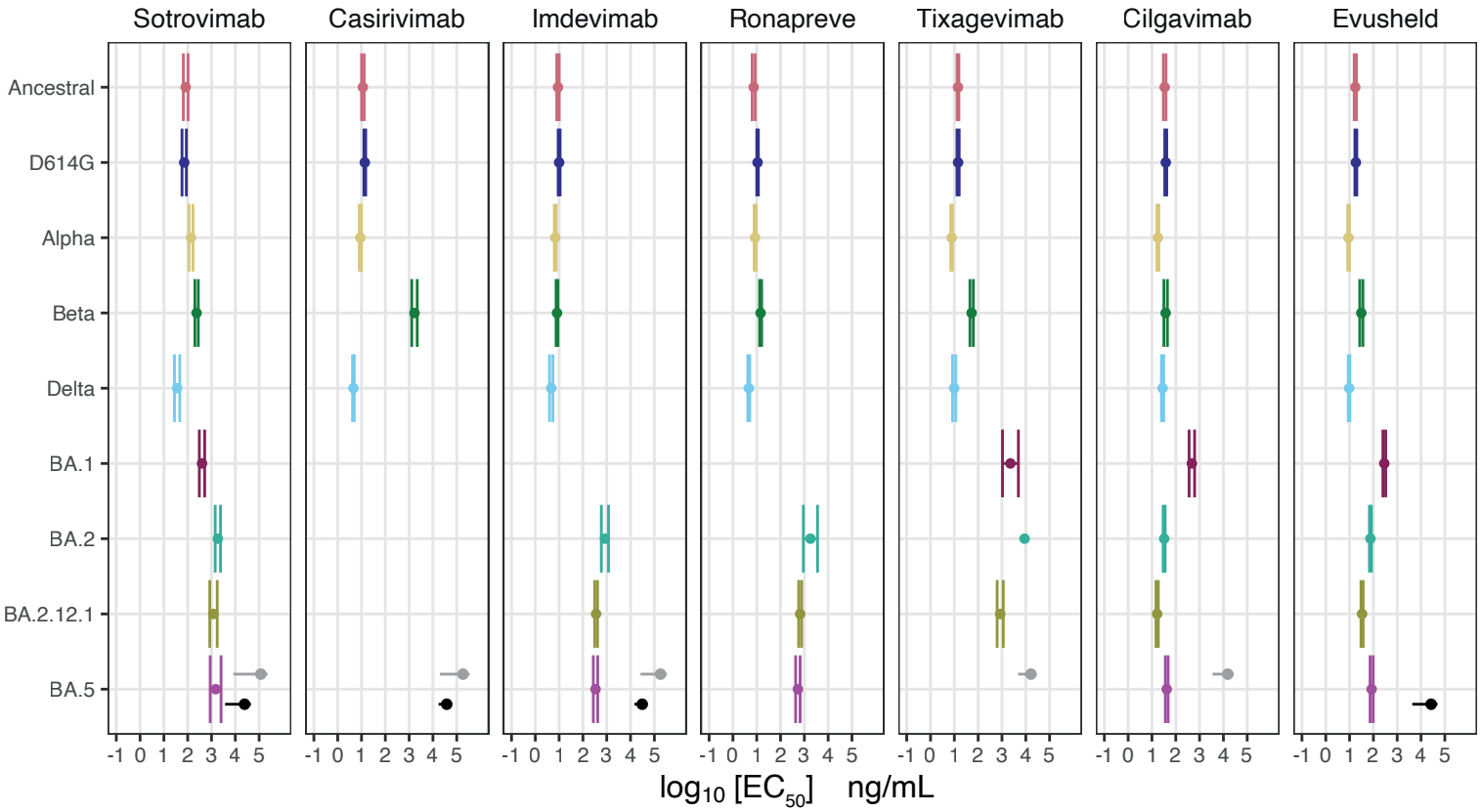

Figure 2. EC_{50} values and confidence intervals for neutralisation of SARS-CoV-2 variants by monoclonal antibodies (mAbs). A summary of neutralisation data shown in Figure 1 is presented here. The EC_{50} value and its 95% confidence interval (error bars) are shown for each combination of monoclonal antibody and SARS-CoV-2 variant as shown in Figure 1. For each mAb, the mean serum concentration at maximum (grey point) and twice its standard deviation (grey error line), and at 28 days post-administration (black points) and twice its standard deviation (black error line) was obtained from its Summary of Product Characteristics (see Table 3) and plotted here for reference.

		Ancestral	D614G	Alpha	Beta	Delta	Omicron				Serum Concentration (ng/ml)	
							BA.1	BA.2	BA.2.12.1	BA.4/5	Max.	28 d.p.i.
Sotrovimab	EC_{50} (ng/ml)	82.3	71.3	137.9	236.5	36.0	399.1	1848.6	1211.2	*1489.6*	117600	24500
	95%CI [Lower,	*65.4*	*57.8*	*133.7*	*200.4*	*27.8*	*308.3*	*1429.2*	*844.0*	*880.9*		
	Upper]	*103.6*	*88.0*	*167.1*	*279.1*	*46.5*	*516.7*	*2391.2*	*1738.2*	*2516.9*		
Casirivimab	EC_{50} (ng/ml)	11.4	13.8	9.0	1680.7	4.6	*(No neutr.)*	*(No neutr.)*	*(No neutr.)*	*(No neutr.)*	182700	37900
	95%CI [Lower,	*10.1*	*12.7*	*8.1*	*1290.1*	*4.2*						
	Upper]	*13.0*	*15.0*	*9.9*	*2189.5*	*5.0*						
Imdevimab	EC_{50} (ng/ml)	9.0	10.0	6.9	8.2	4.7	*(No neutr.)*	839.4	356.8	338.5	181700	31000
	95%CI [Lower,	*8.0*	*9.1*	*6.3*	*7.5*	*3.9*		*594.6*	*310.4*	*273.8*		
	Upper]	*10.1*	*11.0*	*7.5*	*9.0*	*5.5*		*1185.2*	*410.1*	*418.6*		
Ronapreve (Casirivimab + Imdevimab)	EC_{50} (ng/ml)	7.4	10.9	8.6	14.6	4.6	*(No neutr.)*	1802.1	663.4	*534.8*	*n.r.*	*n.r.*
	95%CI [Lower,	*6.4*	*10.1*	*7.8*	*13.2*	*4.2*		*907.2*	*576.6*	*430.9*		
	Upper]	*8.7*	*11.7*	*9.4*	*16.1*	*5.1*		*3579.9*	*763.4*	*663.7*		
Tixagevimab	EC_{50} (ng/ml)	14.2	14.4	7.7	53.2	9.8	2268.5	8914.9	842.7	*(No neutr.)*	16500	*n.r.*
	95%CI [Lower,	*13.1*	*12.9*	*7.1*	*45.1*	*8.4*	*1051.9*	*n.d.*	*638.1*			
	Upper]	*15.5*	*15.9*	*8.4*	*62.7*	*61.6*	*4892.2*	*n.d.*	*1130.7*			
Cilgavimab	EC_{50} (ng/ml)	34.2	38.0	17.8	37.6	28.0	473.4	32.6	16.6	41.7	15300	*n.r.*
	95%CI [Lower,	*30.1*	*34.6*	*16.2*	*31.7*	*25.0*	*362.6*	*29.5*	*14.8*	*36.5*		
	Upper]	*38.8*	*41.8*	*19.5*	*44.6*	*31.3*	*617.9*	*35.9*	*18.6*	*47.6*		
Evusheld (Cilgavimab + Tixagevimab)	EC_{50} (ng/ml)	17.4	18.4	9.1	31.1	9.6	287.2	75.3	33.5	84.3	*n.r.*	26700
	95%CI [Lower,	*15.6*	*16.8*	*8.4*	*26.4*	*8.8*	*250.5*	*68.4*	*30.1*	*72.7*		
	Upper]	*19.5*	*20.1*	*9.8*	*36.3*	*10.4*	*329.4*	*82.9*	*37.2*	*97.8*		

Table 1. EC_{50} values and confidence intervals for neutralisation of SARS-CoV-2 variants by monoclonal antibodies (mAbs). A summary of neutralisation data shown in Figure 1 and Figure 2 is shown. For reference, the mean serum concentration at maximum and 28 days post-administration for each mAb was obtained from its Summary of Product Characteristics and noted here for reference (see Table 3).

		Ancestral	D614G	Alpha	Beta	Delta	Omicron				Serum Concentration (IU/ml)	
							BA.1	BA.2	BA.2.12.1	BA.4/5	Max.	28 d.p.i.
Sotrovimab	EC_{50} (**IU**/ml)	3685	4256	2200	1283	8436	760	164	251	204	2.58	12.38
	95%CI [Lower,	*4637*	*5253*	*2668*	*1514*	*10900*	*984*	*212*	*359*	*344*		
	Upper]	*2928*	*3449*	*1815*	*1087*	*6529*	*587*	*127*	*175*	*121*		
Casirivimab	EC_{50} (**IU**/ml)	26540	22030	33893	181	66378	*(No neutr.)*	*(No neutr.)*	*(No neutr.)*	*(No neutr.)*	1.66	8.00
	95%CI [Lower,	*30064*	*23961*	*37589*	*235*	*72225*						
	Upper]	*23406*	*20250*	*30549*	*139*	*61159*						
Imdevimab	EC_{50} (**IU**/ml)	33856	30274	44027	37129	65096	*(No neutr.)*	361	850	896	1.67	9.79
	95%CI [Lower,	*38109*	*33189*	*48150*	*40609*	*76991*		*510*	*977*	*1108*		
	Upper]	*30064*	*27627*	*40232*	*33931*	*55054*		*256*	*740*	*725*		
Ronapreve (Casirivimab + Imdevimab)	EC_{50} (**IU**/ml)	40772	27907	35479	20820	65376	*(No neutr.)*	168	457	567	*n.r.*	*n.r.*
	95%CI [Lower,	*47398*	*30064*	*39091*	*22946*	*71883*		*334*	*526*	*704*		
	Upper]	*35069*	*25927*	*32237*	*18900*	*59480*		*85*	*397*	*457*		
Tixagevimab	EC_{50} (**IU**/ml)	21317	21139	39345	5703	30828	134	34	360	*(No neutr.)*	18.38	*n.r.*
	95%CI [Lower,	*23209*	*23461*	*42725*	*6722*	*36070*	*288*	*n.d.*	*483*			
	Upper]	*19571*	*19042*	*36285*	*4839*	*26378*	*62*	*n.d.*	*268*			
Cilgavimab	EC_{50} (**IU**/ml)	8883	7981	17080	8072	10845	641	9319	18307	7280	19.83	*n.r.*
	95%CI [Lower,	*10091*	*8777*	*18714*	*9584*	*12124*	*837*	*10269*	*20496*	*8320*		
	Upper]	*7818*	*7257*	*15588*	*6797*	*9704*	*491*	*8457*	*16353*	*6370*		
Evusheld (Cilgavimab + Tixagevimab)	EC_{50} (**IU**/ml)	17414	16513	33482	9745	31764	1056	4030	9055	3600	*n.r.*	11.36
	95%CI [Lower,	*19445*	*18099*	*36285*	*11370*	*34393*	*1211*	*4438*	*10065*	*4175*		
	Upper]	*15588*	*15062*	*30922*	*8354*	*29309*	*921*	*3660*	*8148*	*3103*		

Table 2. EC_{50} values and confidence intervals (reported in International Units) for neutralisation of SARS-CoV-2 variants by monoclonal antibodies (mAbs), calibrated to the First WHO International Standard for anti-SARS-CoV-2 immunoglobulin. A summary of neutralisation data shown in Figure 1 and Figure 2 is shown. For reference, the mean serum concentration at maximum and 28 days post-administration for each mAb was obtained from its Summary of Product Characteristics and noted here for reference (see Table 3).

mAb	Timept.	Avg	SD	CV	Unit	Source of Information	Date Accessed	Dose	Notes
Sotrovimab	c28	24.5	10.388	42.40%	µg/mL	https://www.medicines.org.uk/emc/product/13097/smpc#gref	24/06/2022	IV 500mg sotrovimab	C29 reported; CV reported + SD back-calculated
Sotrovimab	cmax	117.6	54.684	46.50%	µg/mL	https://www.medicines.org.uk/emc/product/13097/smpc#gref	24/06/2022	IV 500mg sotrovimab	CV reported + SD back-calculated
Casirivimab	c28	37.9	10.33		mg/L	https://www.medicines.org.uk/emc/product/12863#gref	24/06/2022	IV 600 mg casirivimab and 600 mg imdevimab	
Casirivimab	cmax	182.7	81.45		mg/L	https://www.medicines.org.uk/emc/product/12863#gref	24/06/2022	IV 600 mg casirivimab and 600 mg imdevimab	
Imdevimab	c28	31	8.24		mg/L	https://www.medicines.org.uk/emc/product/12863#gref	24/06/2022	IV 600 mg casirivimab and 600 mg imdevimab	
Imdevimab	cmax	181.7	77.78		mg/L	https://www.medicines.org.uk/emc/product/12863#gref	24/06/2022	IV 600 mg casirivimab and 600 mg imdevimab	
Tixagevimab	cmax	16.5	5.874	35.60%	µg/mL	https://www.gov.uk/government/publications/regulatory-approval-of-evusheld-tixagevimabcilgavimab/summary-of-product-characteristics-for-evusheld	24/06/2022	IM 150mg tixagevimab and 150mg cilgavimab	Cmax at 14d; CV reported + SD back-calculated
Cilgavimab	cmax	15.3	5.8905	38.50%	µg/mL	https://www.gov.uk/government/publications/regulatory-approval-of-evusheld-tixagevimabcilgavimab/summary-of-product-characteristics-for-evusheld	24/06/2022	IM 150mg tixagevimab and 150mg cilgavimab	Cmax at 14d; CV reported + SD back-calculated
Evusheld	c28	26.7	11.2		µg/mL	https://www.gov.uk/government/publications/regulatory-approval-of-evusheld-tixagevimabcilgavimab/summary-of-product-characteristics-for-evusheld	24/06/2022	IM 150mg tixagevimab and 150mg cilgavimab	C29 reported

Table 3. Sources of data for mean serum concentrations of monoclonal antibodies.

Supplementary Methods

Monoclonal antibodies

Sotrovimab, casivirimab and imdevimab (together Ronapreve, Regeneron) were obtained from the pharmacy at University College Hospitals NHS Foundation Trust. Tixagevimab and cilgavimab (together Evusheld, AstraZeneca), were obtained directly from the manufacturer.

Virus variants and culture

The Eng02 isolate was obtained from Public Health England and contains an identical spike to the ancestral virus first observed in Wuhan, China in 2019. The D614G, Alpha, Beta, Delta, and Omicron isolates used were the same as previously, and our viral culture technique is unchanged[7]. The SARS-CoV-2 B.1.1.7 isolate ("Alpha") was hCoV-19/England/ 204690005/2020, which carries the D614G, Δ69-70, Δ144, N501Y, A570D, P681H, T716I, S982A and D1118H mutations in Spike [25], and was obtained from Public Health England (PHE), UK, through Prof. Wendy Barclay, Imperial College London, London, UK via the Genotype-to-Phenotype National Virology Consortium (G2P-UK). The B.1.617.2 ("Delta") isolate was MS066352H (GISAID accession number EPI_ISL_1731019), which carries the T19R, K77R, G142D, Δ156- 157/R158G, A222V, L452R, T478K, D614G, P681R, D950N mutations in Spike, and was kindly provided by Prof. Wendy Barclay, Imperial College London, London, UK via G2P-UK. The Omicron BA.1 isolate was M21021166, which carries the A67V, Δ69-70, T95I, Δ142-144, Y145D, Δ211, L212I, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, A701V, N764K, D796Y, N856K, Q954H, N969K, and L981F mutations in Spike, and was kindly provided by Prof. Gavin Screaton, University of Oxford, Oxford, UK via G2P-UK. The Omicron BA.2 isolate carries the T19I, Δ24-26, A27S, G142D, V213G, G339D, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, S477N, T478K, E484A, Q493R, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, and N969K mutations in Spike and was obtained from a Legacy study participant. The Omicron BA.2.12.1 isolate carries the L452Q and S704L mutations in Spike, in addition to the BA.2 mutations listed previously, and was kindly provided by Prof. Gavin Screaton, University of Oxford, Oxford, UK. The Omicron BA.5 isolate carries the T19I, Δ24-26, A27S, Δ69-70, G142D, V213G, G339D, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, L452R, S477N, T478K, E484A, F486V, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, and N969K mutations in Spike was obtained from the laboratory of Alex Sigal, Africa Health Research Institute, Durban, South Africa.

All viral isolates were propagated in Vero V1 cells. Briefly, 50% confluent monolayers of Vero V1 cells were infected with the given SARS CoV-2 strains at an MOI of approx. 0.001. Cells were washed once with DMEM (Sigma; D6429), then 5 ml virus inoculum made up in DMEM was added to each T175 flask and incubated at room temperature for 30 minutes. DMEM + 1% FCS (Biosera; FB-1001/500) was added to each flask. Cells were incubated at 37° C, 5% CO_2 for 4 days until extensive cytopathogenic effect was observed. Supernatant was harvested and clarified by centrifugation at 2000 rpm for 10 minutes in a benchtop centrifuge. Supernatant was aliquoted and frozen at -80°C, and batches were titrated by plaque assay and sequence-validated prior to use.

High-throughput live virus microneutralisation assay

High-throughput live virus microneutralisation assays were performed as previously described[26]. In brief, Vero E6 cells (Institut Pasteur) at 90-100% confluency were infected with given SARS-CoV-2 variants in 384-well format, in the presence of serial dilutions of patient serum samples or monoclonal antibodies. 24 hours after infection, cells were fixed with 4% final Formaldehyde, permeabilised with 0.2% TritonX-100, 3% BSA in PBS (v/v), and stained for SARS-CoV-2 N protein using a Biotin-labelled-CR3009 antibody produced in-house in conjunction with a 488-conjugated Streptavidin (Invitrogen S32354), and cellular DNA using DAPI[27]. Whole-well imaging at 5x was carried out using an Opera Phenix (Perkin Elmer) and fluorescent areas and intensity calculated using the Phenix-associated software Harmony (Perkin Elmer). Infection was estimated from the measured area of infected cells/total area occupied by all cells. The maximal infection level was determined experimentally for each plate with virus-only control wells (100%). Percentages of maximal infection are reported after normalisation to the virus-only control wells.

Data analysis, statistics, and availability

Data analysis was carried out in R. For each monoclonal:VOC combination a 4 parameter fit was modelled, using *drm* from the *drc* package[28], with the following adjustments:

- A lower limit of 0 for the bottom of the curve, reflecting 0% of maximal infection
- An upper limit of 110 for the top of the curve, expecting a y intercept <110% of maximal infection.
- A lower limit of 0.1 and an upper limit of 1.5 was applied to Hill slopes.

For curve generation, a sequence of 100 points between 10^{-1} and 10^{5} (evenly in $\log_{10}$-space) were used to predict y values (% of maximal infection) with each model, alongside 95% confidence intervals, using *predict*. The function *drc* was used to calculate EC_{50} values, with 95% confidence intervals. Model fitting was simplified using the *purrr* package to allow a single model definition to be applied to all VOC:mAb combinations, via *group_by(variant, mAb)*.

Graphs were generated using the *ggplot2* package in R. All data and full R code to produce all figures are freely-available online on Github:
https://github.com/davidlvb/Crick-UCLH-Legacy-Monoclonals-2022-10
Conversion of EC_{50} values to International Units was carried out using the WHO International Standard (IS) for anti-SARS-CoV-2 immunoglobulin[8] (human – NIBSC code 20/136) or a pre-calibrated internal standard, and by dividing the sample titre by the International Standard titre then multiplying by 1000 IU/ml (the expected EC_{50} of the international standard against ancestral SARS-CoV-2).

Ethics

The Legacy study was approved by London Camden and Kings Cross Health Research Authority (HRA) Research and Ethics committee (REC) IRAS number 286469 and sponsored by University College London.

Role of the funding source

This work was undertaken at UCLH/UCL who received a proportion of funding from the National Institute for Health Research (NIHR) University College London Hospitals Department of Health's NIHR Biomedical Research Centre (BRC). EW and BW are supported by the Centre's funding scheme. This work was supported jointly by the BRC and core funding from the Francis Crick Institute, which receives its funding from Cancer Research UK, the UK Medical Research Council, and the Wellcome Trust. DLVB is additionally supported by the Genotype-to-Phenotype National Virology Consortium (G2P-UK) via UK Research and Innovation and the UK Medical Research Council. The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding authors had full access to all the data and the final responsibility to submit for publication.

Declaration of interests

CSw reports interests unrelated to this Correspondence: grants from BMS, Ono-Pharmaceuticals, Boehringer-Ingelheim, Roche-Ventana, Pfizer and Archer Dx, unrelated to this Correspondence; personal fees from Genentech, Sarah Canon Research Institute, Medicxi, Bicycle Therapeutics, GRAIL, Amgen, AstraZeneca, BMS, Illumina, GlaxoSmithKline, MSD, and Roche-Ventana, unrelated to this Correspondence; and stock options from Apogen Biotech, Epic Biosciences, GRAIL, and Achilles Therapeutics, unrelated to this Correspondence. SG reports funding from AstraZeneca to evaluate monoclonal antibodies subsequent to this work. MB is a local PI on LUNAR, a GSK sotrovimab monitoring

study, with no personal financial reward. DLVB reports grants from AstraZeneca unrelated to this Correspondence. All other authors declare no competing interests.

Acknowledgements

This research was funded in whole, or in part, by the Wellcome Trust [FC011104, FC011233, FC001030, FC001159, FC001827, FC001078, FC001099, FC001169]. For the purpose of Open Access, the author has applied a CC BY public copyright licence to any Author Accepted Manuscript version arising from this submission. The authors would like to thank all the study participants, the staff of the NIHR Clinical Research Facility at UCLH including Kirsty Adams and Marivic Ricamara. We would like to thank Jules Marczak, Gita Mistry, Simon Caiden and the staff of the Scientific Technology Platforms (STPs) and COVID-19 testing pipeline at the Francis Crick Institute. We thank Tom Peacock of Imperial College London and Laurie Tomlinson of the London School for Hygeine and Tropical Medicine for sharing data and discussions on this manuscript. We thank Prof. Wendy Barclay of Imperial College and the wider Genotype to Phenotype consortium for the Alpha and Delta strains used in this study, and Max Whiteley and Thushan I de Silva at The University of Sheffield and Sheffield Teaching Hospitals NHS Foundation Trust for providing source material. We thank Prof. Gavin Screaton of the University of Oxford for the Omicron BA.1 strain used in this study. We thank Khadija Kahn and Alex Sigal of the Africa Health Research Institute for the Beta and Omicron BA.5 strain used in the study, and Ann-Katrin Reuschl and Clare Joly of University College London for propagation. We thank Taylor Cohen and Gavin Koh of AstraZeneca for providing cilgavimab and tixagavimab. This work was supported by the National Institute for Health Research University College London Hospitals Department of Health's NIHR Biomedical Research Centre (BRC), as well as by the UK Research and Innovation and the UK Medical Research Council (MR/W005611/1), and by the Francis Crick Institute which receives its core funding from Cancer Research UK (FC011104, FC011233, FC001030, FC001159, FC001827, FC001078, FC001099, FC001169), the UK Medical Research Council (FC011104, FC011233, FC001030, FC001159, FC001827, FC001078, FC001099, FC001169), and the Wellcome Trust (FC011104, FC011233, FC001030, FC001159, FC001827, FC001078, FC001099, FC001169).

Supplementary References

1 COVID-19 Response: Living with COVID-19. Gov.uk. 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, Tazare J, *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 May 23. DOI:10.1101/2022.05.22.22275417.

3 World Health Organization. WHO/2019-nCoV/therapeutics/2022.4 Therapeutics and COVID-19: living guideline. 2022.

4 World Health Organization. WHO/2019-nCoV/therapeutics/2022.5 Therapeutics and COVID-19: living guideline. 2022.

5 Wall EC, Wu M, Harvey R, *et al.* Neutralising antibody activity against SARS-CoV-2 VOCs B.1.617.2 and B.1.351 by BNT162b2 vaccination. *Lancet* 2021; published online June 3. DOI:10.1016/S0140-6736(21)01290-3.

6 Wall EC, Wu M, Harvey R, *et al.* AZD1222-induced neutralising antibody activity against SARS-CoV-2 Delta VOC. *Lancet* 2021; published online June 28. DOI:10.1016/S0140-6736(21)01462-8.

7 Wu M, Wall EC, Carr EJ, *et al.* Three-dose vaccination elicits neutralising antibodies against omicron. *Lancet* 2022; published online Jan 19. DOI:10.1016/S0140-6736(22)00092-7.

8 Mattiuzzo 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. https://cdn.who.int/media/docs/default-source/biologicals/ecbs/bs-2020-2403-sars-cov-2-ab-ik-17-nov-2020_4ef4fdae-e1ce-4ba7-b21a-d725c68b152b.pdf?sfvrsn=662b46ae_8&download=true (accessed July 13, 2021).

9 Bentley EM, Atkinson E, Rigsby 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. https://cdn.who.int/media/docs/default-source/biologicals/bs-documents-(ecbs)/2022-documents/new-2022-document-susan/bs-2022.2427_mattiuzzo-g._sars-cov-2_ab_2ndisandrpfor-voc_final.pdf?sfvrsn=90585abb_1&download=true.

10 Lempp FA, Soriaga LB, Montiel-Ruiz M, *et al.* Lectins enhance SARS-CoV-2 infection and influence neutralizing antibodies. *Nature* 2021; **598**: 342–7.

11 US Food and Drug Administration. Fact sheet for healthcare providers Emergency Use Authorization (EUA) of sotrovimab authorized use. 2022; published online March. https://www.fda.gov/media/149534/download (accessed May 6, 2022).

12 Center for Drug Evaluation, Research. FDA updates Sotrovimab emergency use authorization. U.S. Food and Drug Administration. 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**: o1009.

14 Sheward DJ, Kim C, Fischbach J, *et al.* Omicron sublineage BA.2.75.2 exhibits extensive escape from neutralising antibodies. bioRxiv. 2022; : 2022.09.16.508299.

15 Bruel T, Hadjadj J, Maes P, *et al.* Serum neutralization of SARS-CoV-2 Omicron sublineages BA.1 and BA.2 in patients receiving monoclonal antibodies. *Nat Med* 2022; published online March 23. DOI:10.1038/s41591-022-01792-5.

16 Hoffmann M, Krüger N, Schulz S, *et al.* The Omicron variant is highly resistant against antibody-mediated neutralization: Implications for control of the COVID-19 pandemic. *Cell* 2022; **185**: 447-456.e11.

17 Planas D, Saunders N, Maes P, *et al.* Considerable escape of SARS-CoV-2 Omicron to antibody neutralization. *Nature* 2021; published online Dec 23. DOI:10.1038/d41586-021-03827-2.

18 MHRA Central Alerting System. Neutralising monoclonal antibody and intravenous antiviral treatments for patients in hospital with COVID-19 infection. MHRA Central Alerting System. 2021; published online Dec 24. https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=103189 (accessed May 6, 2022).

19 Takashita E, Yamayoshi S, Simon V, *et al.* Efficacy of Antibodies and Antiviral Drugs against Omicron BA.2.12.1, BA.4, and BA.5 Subvariants. *N Engl J Med* 2022; **387**: 468–70.

20 Arora P, Kempf A, Nehlmeier I, *et al.* Augmented neutralisation resistance of emerging omicron subvariants BA.2.12.1, BA.4, and BA.5. Lancet Infect. Dis. 2022; **22**: 1117–8.

21 Cao Y, Yisimayi A, Jian F, *et al.* BA.2.12.1, BA.4 and BA.5 escape antibodies elicited by Omicron infection. *Nature* 2022; **608**: 593–602.

22 Hentzien M, Autran B, Piroth L, Yazdanpanah Y, Calmy A. A monoclonal antibody stands out against omicron subvariants: a call to action for a wider access to bebtelovimab. Lancet Infect. Dis. 2022; **22**: 1278.

23 Nichols RM, Deveau C, Upadhyaya H. Bebtelovimab: considerations for global access to treatments during a rapidly evolving pandemic. *Lancet Infect Dis* 2022; published online Sept 26. DOI:10.1016/S1473-3099(22)00592-8.

24 US Food and Drug Administration. FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR BEBTELOVIMAB. 09/2022 https://www.fda.gov/media/156152/download (accessed Sept 30, 2022).

25 Brown JC, Goldhill DH, Zhou J, *et al.* Increased transmission of SARS-CoV-2 lineage B.1.1.7 (VOC 2020212/01) is not accounted for by a replicative advantage in primary airway cells or antibody escape. Cold Spring Harbor Laboratory. 2021; : 2021.02.24.432576.

26 Faulkner N, Ng KW, Wu MY, *et al.* Reduced antibody cross-reactivity following infection with B.1.1.7 than with parental SARS-CoV-2 strains. *Elife* 2021; **10**. DOI:10.7554/eLife.69317.

27 van den Brink EN, Ter Meulen J, Cox F, *et al.* Molecular and biological characterization of human monoclonal antibodies binding to the spike and nucleocapsid proteins of severe acute respiratory syndrome coronavirus. *J Virol* 2005; **79**: 1635–44.

28 Ritz C, Baty F, Streibig JC, Gerhard D. Dose-Response Analysis Using R. *PLoS One* 2015; **10**: e0146021.