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.

with $B.1_{pp}$ (9·4× reduction for BA.2, 11·7× reduction for BA.2.75, and 39·0× reduction for BA.4/BA.5). By contrast, breakthrough infection during the omicron wave induced higher omicron sublineage neutralisation, although neutralisation of $BA.2.75_{pp}$ and $BA.4/BA.5_{pp}$ was significantly lower as compared with $BA.2_{pp}$ (2·8× reduction for $BA.2.75_{pp}$ and 3·6× reduction for $BA.4/BA.5_{pp}$; appendix p 2).

Although our results await confirmation with authentic virus and primary cells, BA.2.75 might be more adept than BA.2 at infecting the lower airways and inducing cell–cell fusion, which could indicate an elevated intrinsic pathogenic potential. Moreover, we identified bebtelovimab (also known as LYCoV-1404) and the cilgavimab–tixagevimab antibody combination as treatments for BA.2.75-infected individuals. The observation that BA.2.75 and BA.4/BA.5 display lower neutralisation sensitivity compared with BA.2 suggests that this trait might enable them to outcompete BA.2 in subpopulations with vaccination or infection-induced immunity. Finally, our data confirm and extend the findings of two recent studies[6,7] and provide evidence that three vaccine doses are required to induce potent neutralising activity against BA.2.75, similar to what has been shown for other omicron sublineages.[8–10]

Published Online October 13, 2022 https://doi.org/10.1016/S1473-3099(22)00663-6

See Online for appendix

AK, IN, SP, and MH conduct contract research (testing of vaccine sera for neutralising activity against SARS-CoV-2) for Valneva unrelated to this work. GMNB was an advisor for Moderna and SP was an advisor for BioNTech, unrelated to this work. SP acknowledges funding by the Federal Ministry of Education and Research (BMBF; grant numbers 01KI2006D, 01KI20328A, and 01KX2021), the EU UNDINE project (grant agreement number 101057100), the Ministry for Science and Culture of Lower Saxony (grant numbers 14-76103-184 and MWK HZI COVID-19), and the German Research Foundation (Deutsche Forschungsgemeinschaft; PO 716/11-1 and PO 716/14-1). MSW received unrestricted funding from Sartorius AG, Lung research. H-MJ received funding from BMBF (grant numbers 01KI2043 and NaFoUniMedCovid19-COVIM: 01KX2021), Bavarian State Ministry for Science and the Arts and Deutsche Forschungsgemeinschaft through the research training groups RTG1660 and TRR130, the Bayerische Forschungsstiftung (Project CORAd), and the Kastner Foundation. GMNB acknowledges funding by German Center for Infection Research (grant number 80018019238) and a European Regional Development Fund (Defeat Corona, grant number ZW7-8515131). All other authors declare no competing interests.

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Omicron sublineage BA.2.75.2 exhibits extensive escape from neutralising antibodies

SARS-CoV-2 omicron sublineage BA.2.75 expanded rapidly in parts of the world, but it has so far not outcompeted BA.5 globally. Despite similar geometric mean neutralising titres (GMT) to BA.5, BA.2.75 remained sensitive to classes of antibodies that BA.5 had escaped,[1,2] suggesting scope for antibody evasion. The emergence of a sublineage of BA.2.75 carrying additional mutations R346T, F486S, and D1199N (BA.2.75.2; figure A; appendix p 1), growing rapidly (appendix p 2), suggested more extensive escape from neutralising antibodies.

F486V contributed to escape in BA.5,[3] mutations at spike residue 346 have occurred in earlier variants,[4,5] and have been specifically highlighted for their capacity to confer additional in escape in omicron.[6] Numerous sublineages of the omicron variant have been detected carrying convergent mutations at position 346. R346S is present in BA.4.7, and R346I in BA.5.9.[7] BA.4.6, carrying R346T and N658S, is currently the dominant 346T-carrying lineage, detected across a wide geographic distribution. Similarly, several lineages are emerging carrying mutations at residue 486, including BA.2.10.4 harbouring a highly mutated spike, including F486P.

Here we report the sensitivity of emerging omicron sublineages BA.2.75.2, BA.4.6, and BA.2.10.4 to neutralisation by a panel of clinically

relevant and preclinical monoclonal antibodies and by serum from blood donated in Stockholm, Sweden. BA.2.75.2 and BA.4.6 both show complete escape from cilgavimab and a combination of cilgavimab and tixagevimab, whereas BA.2.10.4 retains some sensitivity to cilgavimab (figure B). Sotrovimab exhibits similarly low potency against BA.5, BA.2.75.2, and BA.2.10.4, with some reduction against BA.4.6. Bebtelovimab still potently neutralises all variants we tested.

To characterise the evolving resistance to immunity at the population level, we evaluated the sensitivity to neutralisation by serum from random blood donors in Stockholm, including a cohort sampled Nov 8–14, 2021 (November 2021 cohort; figure C), before the emergence of the omicron variant; a cohort sampled April 11–17, 2022 (April 2022 cohort; figure D), after both a large wave of infections (driven by BA.1 then BA.2) and the rollout of third vaccine doses; and a cohort sampled Aug 29 to Sept 4, 2022 (September 2022 cohort; figure E), after the spread of BA.5.

In only the September 2022 cohort, ancestral B.1 titres were at a similar level to those against omicron

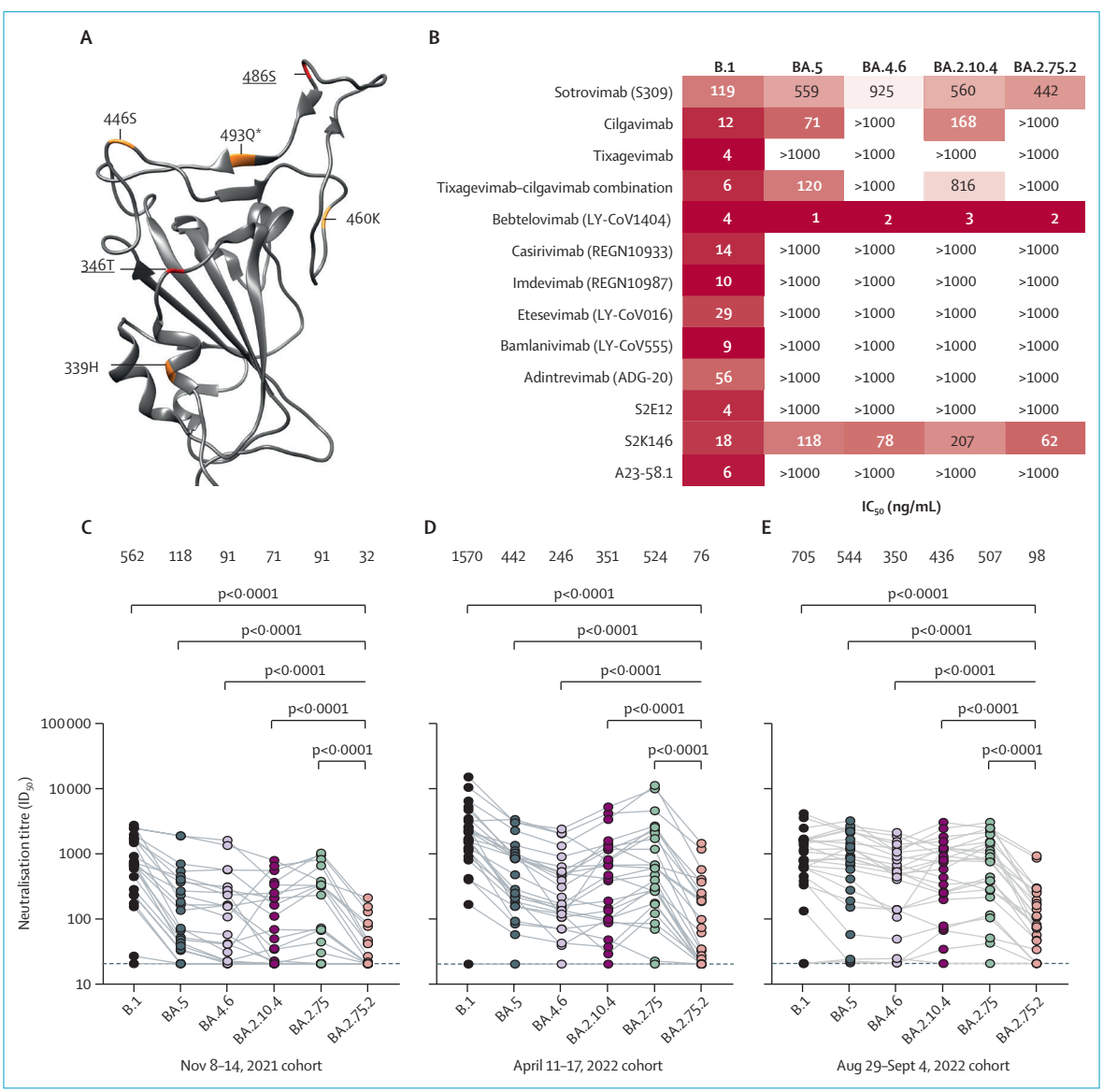

***Figure*: BA.2.75.2 escapes neutralising antibodies**

(A) Differences from BA.2 in BA.2.75 (orange), and BA.2.75.2 (red, underlined), depicted upon the SARS-CoV-2 BA.2 receptor binding domain (pdb:7UB0). Sensitivity of SARS-CoV-2 omicron sublineages and ancestral B.1 (D614G) to neutralisation by monoclonal antibodies (B), and randomly sampled sera from blood donated in Stockholm, Sweden, between Nov 8–14, 2021 (n=25; C), April 11–17, 2022 (n=25; D), and Aug 29 to Sept 4, 2022 (n=25; E). Sera with neutralisation less than 50% at the lowest dilution tested (20) are plotted as 20 (dotted line). IC_{50}=50% inhibitory concentration. ID_{50}=50% inhibitory dilution. *Indicates reversion.

variants (figure E), potentially as a result of omicron infections. There was a significant difference between the neutralisation of BA.5 and B.1 in the November 2021 and April 2022 cohorts (p<0·0001); however, neutralisation of the two variants was not statistically different in the September 2022 cohort. BA.4.6 (GMT 350 [95% CI 195–629]) and BA.2.10.4 (GMT 436 [248–767]) were moderately more resistant to neutralisation than BA.5 (GMT 544 [287–1033]).

Across all three timepoints, neutralisation of BA.2.75.2 by serum antibodies was significantly lower than all other variants tested (figure C, D, and E). Both R346T and F486S mutations contributed to the significantly enhanced resistance of BA.2.75.2 compared with BA.2.75 (appendix p 3). 14 (56%) of 25 samples from the November 2021 cohort had ID_{50} titres against BA.2.75.2 that were below the limit of detection (<20). In samples from April 2022 and September 2022 cohorts, BA.2.75.2 was neutralised with a GMT approximately 6·5-times lower than that of the currently dominant BA.5 sublineage, representing the most resistant variant characterised at the time of writing (Sept 19, 2022). Taken together, these data identify profound antibody escape by the emerging omicron sublineage BA.2.75.2, suggesting that it effectively evades current humoral immunity in the population.

STR is a cofounder of and held shares in deepCDR Biologics, which has been acquired by Alloy Therapeutics. DJS, GBKH, and BM have intellectual property rights associated with antibodies that neutralise omicron variants. All other authors declare no competing interests.

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