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.

evasion, especially against convalescents from BA.4 and BA.5 breakthrough infection, contributes to the emergence and rapid spread of multiple Arg346-mutated BA.4 and BA.5 sublineages. The decreased neutralisation titres of plasma samples from BA.5 breakthrough-infection convalescents indicate worrisome potential reinfection of BA.4.6 after the recovery from BA.4 or BA.5 infection. Importantly, individuals that received Evusheld as long-term prophylaxis, especially those that are immunodeficient or exhibit high-risk comorbidities, are at particular risk of those subvariants. Also, BA.4 and BA.5-based vaccine boosting strategies should be evaluated in light of the prevalence of these BA.4 and BA.5 subvariants.

YC and XSX are co-founders of Singlomics Biopharmaceuticals and inventors of patents associated with SARS-CoV-2 neutralising antibodies. All other authors declare no competing interests. FJ and YY contributed equally.

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Lung cell entry, cell–cell fusion capacity, and neutralisation sensitivity of omicron sublineage BA.2.75

The SARS-CoV-2 omicron (B.1.1.529) variant evades antibody-mediated neutralisation with high efficiency, challenging efforts to contain the COVID-19 pandemic through vaccination. Several omicron sublineages evolved since January, 2022, with some displaying elevated neutralisation resistance over early sublineages like BA.1, BA.1.1, and BA.2.[1,2] Recently, the novel omicron sublineage BA.2.75, which has a unique constellation of spike protein mutations (appendix p 2), was identified in India and the proportion of infections due to BA.2.75 is steadily increasing.[3]

We investigated the host cell entry and neutralisation sensitivity of BA.2.75 using pseudovirus particles (pp), which adequately model SARS-CoV-2 host cell entry and its neutralisation.[4] Particles bearing BA.2.75 spike ($BA.2.75_{pp}$) entered Calu-3 human lung cells more efficiently than $BA.2_{pp}$ (1·6× increase) but similarly to $BA.4/BA.5_{pp}$ and less efficiently than $B.1_{pp}$, which represents the virus circulating early in the pandemic (January–May, 2020; 1·7× reduction). For the remaining cell lines, entry efficiency of $BA.2_{pp}$, $BA.2.75_{pp}$, and $BA.4/BA.5_{pp}$ were similar (appendix p 2).

The ability of the SARS-CoV-2 spike protein to fuse cells and cause the formation of multinucleated giant cells is believed to contribute to pathogenesis.[5] In our quantitative fusion assay, cell–cell fusion capacity of BA.2.75 spike was higher than BA.2 spike (1·5× increase), similar to BA.4/BA.5 spike, and lower than B.1 spike (1·2× reduction) and the delta (B.1.617.2) variant spike (1·6× reduced; appendix p 2).

Next, we assessed BA.2.75 neutralisation by monoclonal antibodies for COVID-19 treatment. Three of ten antibodies did not neutralise $BA.2.75_{pp}$, and seven antibodies showed reduced neutralisation compared with $B.1_{pp}$ (3·7–922× reduction), with bebtelovimab and cilgavimab neutralising $BA.2.75_{pp}$ most efficiently (appendix p 2).

Finally, we investigated BA.2.75 neutralisation by antibodies induced after vaccination or breakthrough infection during the delta (October, 2021, to January, 2022) or early omicron (February–May, 2022, dominated by BA.1 and BA.2) waves in Germany. While the two-dose BNT162b2 primary immunisation schedule did not induce robust neutralising activity against $BA.2_{pp}$, $BA.2.75_{pp}$, or $BA.4/BA.5_{pp}$, a third dose of the vaccine strongly increased omicron sublineage neutralisation. However, neutralisation of $BA.2.75_{pp}$ and $BA.4/BA.5_{pp}$ was moderately reduced compared with $BA.2_{pp}$ (2·1× reduction for $BA.2.75_{pp}$ and 2·2× reduction for $BA.4/BA.5_{pp}$), and breakthrough infection during the delta wave induced substantially less neutralising activity against all three omicron sublineages as compared

Published **Online** September 15, 2022 https://doi.org/10.1016/S1473-3099(22)00591-6

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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