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.

Neutralisation sensitivity of the SARS-CoV-2 XBB.1 lineage

Co-infection with multiple SARS-CoV-2 lineages can result in recombination of the viral genomes and the emergence of novel, recombinant SARS-CoV-2 lineages.[1–4] In January, 2022, the recombinant SARS-CoV-2 XBB lineage was first detected in India and incidence is increasing in Asia and Europe.[5] The XBB lineage is the result of recombination of two omicron variant sublineages, BJ.1 and BM.1.1.1, and the breakpoint is located in the gene for the spike protein (appendix p 10),[6] which is responsible for host cell entry and constitutes the target of neutralising antibodies. Five major XBB sublineages (XBB.1 to XBB.5) have evolved so far, and sublineage XBB.1 accounts for most cases.[5]

We report an initial assessment of the ability of the SARS-CoV-2 XBB.1 lineage to enter host cells and to evade antibody-mediated neutralisation. For this, we used spike-protein-carrying pseudovirus particles ($_{pp}$) that represent a suitable model to study host-cell entry of SARS-CoV-2 and its neutralisation.[7] Particles pseudotyped with the spike protein of the ancestral B.1 ($B.1_{pp}$) or the currently dominating omicron BA.5 ($BA.5_{pp}$) lineage were used for comparison. Compared with $B.1_{pp}$, $BA.5_{pp}$ entered Vero cells (kidney cells of the African green monkey) with 2·2 times higher efficiency and 293T cells (human kidney cells) with 5·3 times higher efficiency, whereas entry into Calu-3 cells (human lung cells) was 1·9 times less efficient compared with $B.1_{pp}$, as expected (appendix p 10).[8] Particles carrying XBB.1 spike protein ($XBB.1_{pp}$) showed significantly reduced efficiency of cell entry compared with $BA.5_{pp}$ for all cell lines analysed (1·7–3·9 times reduced) and compared with $B.1_{pp}$ for Calu-3 cells (3·4 times reduced), whereas entry efficiency of $XBB.1_{pp}$ and $B.1_{pp}$ was similar for 293T and Vero cells (1·3–1·4 times increased efficiency of $XBB.1_{pp}$; appendix p 10).

We analysed the sensitivity of $XBB.1_{pp}$ to neutralisation by monoclonal antibodies (mAbs) and mAb cocktails that are in clinical use (or for which clinical use has been stopped) or in development for COVID-19 prophylaxis and therapy (figure A). All tested mAbs and mAb cocktails efficiently neutralised $B.1_{pp}$ (effective concentration 50 [EC_{50}] 1–2378 ng/mL), whereas for $XBB.1_{pp}$, only sotrovimab (EC_{50} 1169 ng/mL) and S2H97 (EC_{50} 26 610 ng/mL) were able to neutralise, and efficiency of

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See Online for appendix

A

	B.1	XBB.1
Single mAbs		
Casirivimab	7	>50 000
Imdevimab	7	>50 000
Bamlanivimab	11	>50 000
Etesevimab	20	>50 000
Cilgavimab	12	>50 000
Tixagevimab	3	>50 000
Amubarvimab	57	>50 000
Romlusevimab	979	>50 000
Sotrovimab	101	1169
Bebtelovimab	2	>50 000
S2H97	2378	26 610
Regdanvimab	1	>50 000
mAb cocktails		
Casirivimab–imdevimab	6	>50 000
Bamlanivimab–etesevimab	11	>50 000
Cilgavimab–tixagevimab	5	>50 000
Amubarvimab–romlusevimab	69	>50 000
	EC_{50} (ng/ml)	

B

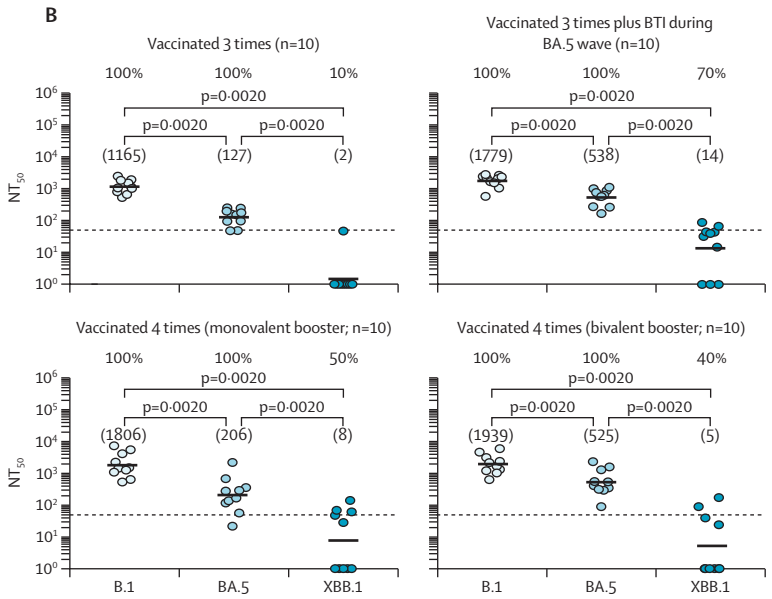

Figure: **Sensitivity of the SARS-CoV-2 XBB.1 lineage to neutralisation by monoclonal antibodies, antibodies induced by vaccination, and antibodies induced by vaccination plus breakthrough infection**

(A) Sensitivity of the SARS-CoV-2 XBB.1 lineage to neutralisation by monoclonal antibodies. Pseudoviruses were preincubated with different concentrations of individual mAb or mAb cocktails before being inoculated onto Vero cells. At 16–18 h after inoculation, pseudovirus entry was analysed, normalised against samples without mAb (0% inhibition), and the EC_{50}, which indicates the mAb concentration required for half-maximal inhibition, was calculated. Data represent the mean of three biological replicates (done with four technical replicates; appendix pp 3–6 and 11–12 for details on the experimental set-up and additional data). (B) Sensitivity of the SARS-CoV-2 XBB.1 lineage to neutralisation by antibodies induced by vaccination or vaccination plus breakthrough infection. Pseudoviruses were preincubated with serially diluted plasma and subsequently inoculated onto Vero cells. At 16–18 h after inoculation, pseudovirus entry was analysed and the NT_{50} was calculated. Data represent geometric mean NT_{50} values from a single biological replicate (done with four technical replicates). Numbers in brackets indicate NT_{50} values and percentages above the graphs represent responder rates (ie, proportion of samples with detectable neutralising activity). Dashed lines indicate the lowest plasma dilution tested. We used the Wilcoxon matched pairs signed rank test to analyse the statistical significance of the effects observed (appendix pp 13–16 for individual data). BTI=breakthrough infection. EC_{50}=effective concentration 50. mAb=monoclonal antibodies. NT_{50}=neutralising titre 50.

neutralisation was reduced by more than 10 times compared with the neutralisation of $B.1_{pp}$.

Finally, we assessed the sensitivity of $XBB.1_{pp}$ to neutralisation by antibodies induced by vaccination or vaccination plus breakthrough infection (figure B; appendix pp 1–2). Plasma of triple vaccinated individuals had almost no detectable neutralising activity against $XBB.1_{pp}$ (neutralising titre 50 [NT_{50}] 2), whereas the neutralising activity against $B.1_{pp}$ was high (NT_{50} 1165) and against $BA.5_{pp}$ was moderate (NT_{50} 127). Next, we measured the plasma of triple vaccinated individuals with breakthrough infection during the BA.5 wave in Germany (June to November, 2022). The plasma samples showed high neutralising activity against $B.1_{pp}$ (NT_{50} 1779), moderate neutralising activity against $BA.5_{pp}$ (NT_{50} 538), and low neutralising activity against $XBB.1_{pp}$ (NT_{50} 14). Similar findings were made for plasma from triple vaccinated individuals who received either monovalent or bivalent (ie, B.1 or B.1 plus BA.5) booster vaccination: $B.1_{pp}$ NT_{50} 1806 for B.1 or 1939 for B.1 plus BA.5; $BA.5_{pp}$ NT_{50} 206 for B.1 or 525 for B.1 plus BA.5; and $XBB.1_{pp}$ NT_{50} 8 for B.1 or 5 for B.1 plus BA.5.

Collectively, our data suggest that the SARS-CoV-2 XBB.1 lineage exhibits an extraordinarily strong ability for antibody evasion, which makes XBB.1 similar to BQ.1 and BQ.1.1;[9] two highly neutralisation-resistant sublineages of omicron that are currently increasing in incidence in several countries worldwide. The finding that most mAbs do not neutralise $XBB.1_{pp}$ highlights that novel mAbs are needed for the treatment of COVID-19 and that other or additional treatment options (eg, paxlovid, molnupiravir, or remdesivir) should be considered in areas with high incidence of the XBB sublineages. The observation that host-cell entry of $XBB.1_{pp}$ is reduced as compared with $BA.5_{pp}$ suggests that the increased ability of XBB.1 to evade antibody-mediated neutralisation might have come at the cost of a moderately reduced efficiency of host-cell entry.

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*Prerna Arora, Anne Cossmann, Sebastian R Schulz, Gema Morillas Ramos, Metodi V Stankov, Hans-Martin Jäck, Georg M N Behrens, Stefan Pöhlmann, *Markus Hoffmann*
mhoffmann@dpz.eu

Infection Biology Unit, German Primate Center, Leibniz Institute for Primate Research, Göttingen 37077, Germany (PA, SP, MH); Faculty of Biology and Psychology, Georg-August University Göttingen, Göttingen, Germany (PA, SP, MH); Department for Rheumatology and Immunology, Hannover Medical School, Hannover, Germany (AC, GMR, MVS, GMNB); Division of Molecular Immunology, Department of Internal Medicine 3, Friedrich-Alexander University of Erlangen-Nürnberg, Erlangen, Germany (SRS, H-MJ); German Centre for Infection Research, Hannover-Braunschweig, Hannover, Germany (GMR, GMNB); Centre for Individualized Infection Medicine, Hannover, Germany (GMNB)

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Stability of hybrid versus vaccine immunity against BA.5 infection over 8 months

The coverage of SARS-CoV-2 vaccination in large parts of the world, together with the high number of breakthrough infections, especially following the emergence of Omicron subvariants, makes hybrid immunity (resulting from vaccine and infection) common. Hybrid immunity, particularly after BA.1 or BA.2 infection, confers substantial protection against the BA.5 infection.[1–3] However, although the waning of protection afforded by natural infection in non-vaccinated individuals or by vaccination has been well documented,[4,5] the stability of hybrid immunity, specifically against the BA.5 subvariant, now dominant in many countries, has not been thoroughly addressed.

We used the Portuguese COVID-19 registry (SINAVE), which includes all notified cases of infection in the