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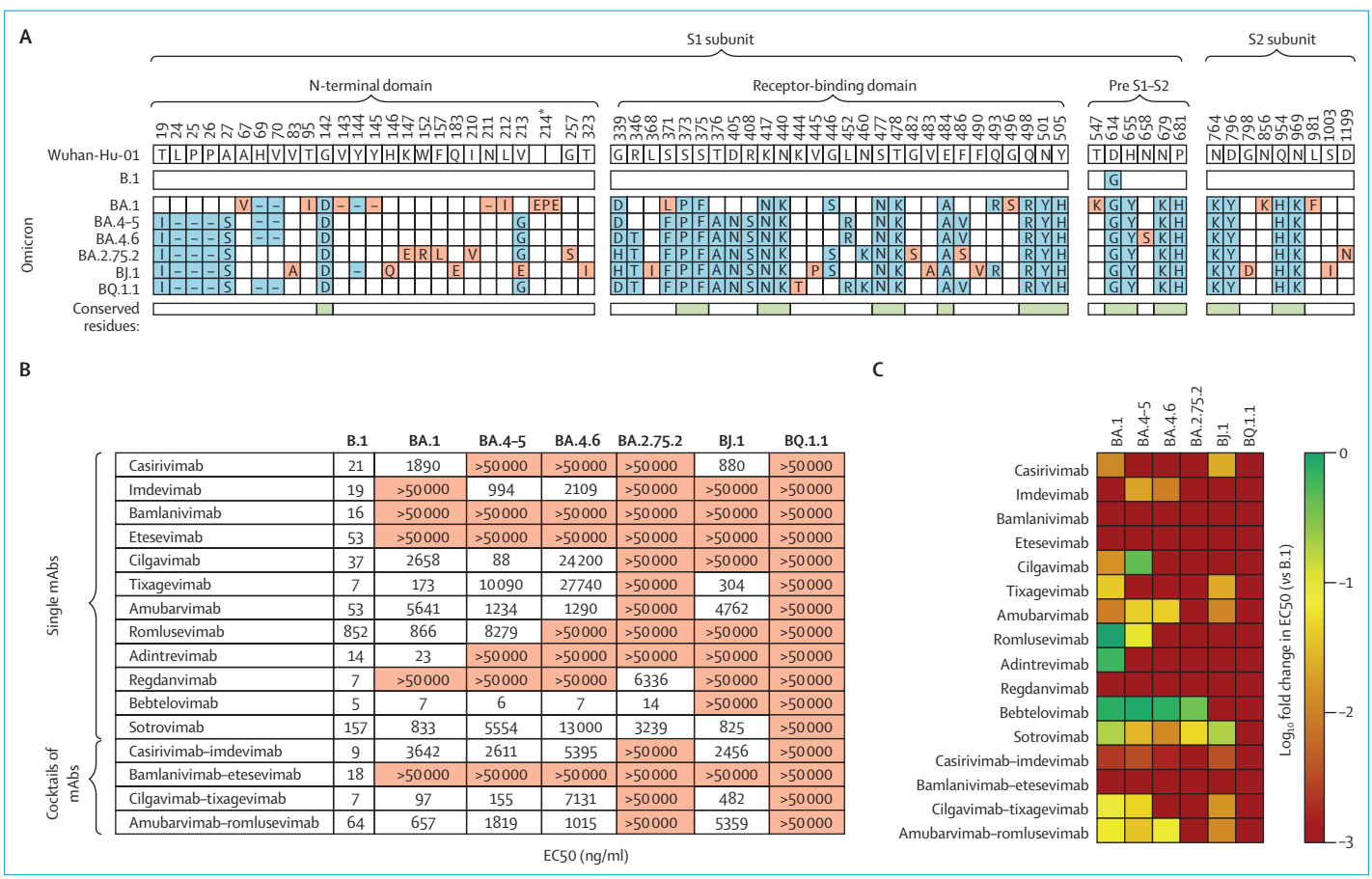
See Online for appendix

Omicron sublineage BQ.1.1 resistance to monoclonal antibodies

Vaccination represents the key strategy to control the COVID-19 pandemic through induction of neutralising antibody responses and T cell-associated immunity that substantially decrease the risk of developing severe disease.[1,2] However, individuals who are immunocompromised (eg, because of comorbidities, high age, or immunosuppressive treatment) might not mount a full adaptive immune response and thus remain susceptible. For individuals at high risk, individual monoclonal antibodies (mAbs) or cocktails of mAbs are administered as prophylaxis or therapy.[3,4] All mAbs currently approved by the US Food and Drug Administration (FDA) or European Medicines Agency (EMA) target the spike (S) protein (appendix pp 1–2).[5] During the course of the COVID-19 pandemic, several SARS-CoV-2 lineages evolved mutations that confer partial or full resistance against some mAbs.[6–9] Consequently, only few mAbs remain suitable for treatment of individuals at high risk, and only bebtelovimab shows high efficacy against multiple omicron sublineages.[8] However, novel omicron sublineages have been detected, harbouring additional S protein mutations within the epitopes of bebtelovimab and other mAbs (figure A; appendix p 11). Novel sublineages include BA.4.6 (with increasing incidence in several countries worldwide), BA.2.75.2 (with increasing incidence in India), BJ.1 (mainly observed in India and Bangladesh; notably BJ.1 is one parental lineage of the currently increasing XBB recombinant), and BQ.1.1 (with increasing incidence in the USA and Europe).

We compared neutralisation of omicron sublineages BA.1, BA.4–5



	B.1	BA.1	BA.4–5	BA.4.6	BA.2.75.2	BJ.1	BQ.1.1
Casirivimab	21	1890	>50000	>50000	>50000	880	>50000
Imdevimab	19	>50000	994	2109	>50000	>50000	>50000
Bamlanivimab	16	>50000	>50000	>50000	>50000	>50000	>50000
Etesevimab	53	>50000	>50000	>50000	>50000	>50000	>50000
Cilgavimab	37	2658	88	24200	>50000	>50000	>50000
Tixagevimab	7	173	10090	27740	>50000	304	>50000
Amubarvimab	53	5641	1234	1290	>50000	4762	>50000
Romlusevimab	852	866	8279	>50000	>50000	>50000	>50000
Adintrevimab	14	23	>50000	>50000	>50000	>50000	>50000
Regdanvimab	7	>50000	>50000	>50000	6336	>50000	>50000
Bebtelovimab	5	7	6	7	14	>50000	>50000
Sotrovimab	157	833	5554	13000	3239	825	>50000
Casirivimab–imdevimab	9	3642	2611	5395	>50000	2456	>50000
Bamlanivimab–etesevimab	18	>50000	>50000	>50000	>50000	>50000	>50000
Cilgavimab–tixagevimab	7	97	155	7131	>50000	482	>50000
Amubarvimab–romlusevimab	64	657	1819	1015	>50000	5359	>50000

***Figure*: Extensive resistance of omicron sublineage B.Q.1.1 to neutralisation by mAbs**
(A) Location of mutations (blue and red) in the spike proteins of SARS-CoV-2 lineages B.1, BA.1, and BA.4–5 (which are identical at the amino acid level), BA.4.6, BA.2.75.2, BJ.1, and BQ.1.1 (numbered according to the spike protein of SARS-CoV-2 Wuhan-Hu-01). Mutations that are unique to only one of the omicron sublineages are highlighted in red and conserved mutations among omicron sublineages are indicated beneath the sequences in green. (B) Pseudovirus particles carrying the indicated S proteins were preincubated with different concentrations of single mAbs or cocktails of mAbs, before being inoculated onto Vero cells. Pseudovirus entry was analysed at 16–18 h post-inoculation, by measuring firefly luciferase activity in cell lysates, and was normalised against samples without any antibodies (0% inhibition). The EC50 was calculated by use of a non-linear regression model. Data represent the mean of three biological replicates (performed with four technical replicates). For additional information see the appendix (p 12). (C) Heatmap indicating the fold change in EC50 compared with B.1 pseudovirus particles. EC50=the concentration required for 50% of maximum inhibition. mAbs=monoclonal antibodies. Pre S1–S2=the domain between the receptor-binding domain and the S1–S2 cleavage site. S=spike. *The BA.1 spike protein contains a unique insertion at position 214 (EPE).

(in which the amino acid sequence of the S protein is identical), BA.4.6, BA.2.75.2, BJ.1 and BQ.1.1 by single mAbs or mAb cocktails that are currently in clinical use, mAbs for which clinical use has been restricted or discontinued, and mAbs currently being evaluated in clinical trials. We used pseudovirus particles ($_{pp}$) that represent a suitable model to investigate SARS-CoV-2 cell entry and its neutralisation.[10] As we expected, pseudovirus particles bearing the BA.1 S protein ($BA.1_{pp}$) were efficiently neutralised by bebtelovimab, adintrevimab, and cilgavimab–tixagevimab (50% effective concentration [EC50] <100 ng/ml), moderately neutralised by tixagevimab, romlusevimab, sotrovimab, and amubarvimab–romlusevimab (EC50 100–1000 ng/ml), and poorly neutralised by casirivimab, cilgavimab, amubarvimab, and casirivimab–imdevimab (EC50 1000–10 000 ng/ml).[7] Furthermore, $BA4–5_{pp}$ were efficiently neutralised by bebtelovimab and cilgavimab, moderately neutralised by imdevimab and cilgavimab–tixagevimab, and poorly neutralised by amubarvimab, romlusevimab, sotrovimab, casirivimab–imdevimab, and amubarvimab–romlusevimab, in line with expectations.[8] For $BA.4.6_{pp}$, bebtelovimab caused efficient neutralisation, whereas poor neutralisation was noted for imdevimab, amubarvimab, casirivimab–imdevimab, cilgavimab–tixagevimab, and amubarvimab–romlusevimab. With $BA.2.75.2_{pp}$, bebtelovimab caused efficient neutralisation, whereas regdanvimab and sotrovimab caused poor neutralisation. For $BJ.1_{pp}$, none of the tested mAbs or mAb cocktails caused high neutralisation, whereas casirivimab, tixagevimab, sotrovimab, and cilgavimab–tixagevimab showed moderate neutralisation, and amubarvimab, casirivimab–imdevimab, and amubarvimab–romlusevimab caused poor neutralisation. Finally, none of the tested mAbs or mAb cocktails caused appreciable neutralisation of $BQ.1.1_{pp}$ (figure B–C; appendix p 12).

Our data reveal that emerging omicron sublineages are resistant to most (ie, BA.4.6, BA.2.75.2, and BJ.1) or all (BQ.1.1) clinically used mAbs. As a consequence, in patients at high risk, treatment with mAbs alone might not provide a therapeutic benefit in regions of the globe in which BQ.1.1 is spreading, suggesting that additional treatment options (eg, paxlovid or molnupiravir) should be considered. Furthermore, novel, broadly active mAbs are urgently needed for prophylactic or therapeutic treatment, or both, in patients at high risk.

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Decline of RSV-specific antibodies during the COVID-19 pandemic

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Hospitalisations due to respiratory syncytial virus (RSV) infections largely decreased after social distancing measures were introduced to control the COVID-19 pandemic. Lifting these measures resulted in out-of-season RSV activity, sometimes exceeding the incidence of hospitalisations observed in regular seasons.[1–3] Declining immunity due to reduced exposure to the virus may contribute to this altered epidemiology.[1,4,5] Bardsley and colleagues[1] showed that the combination of laboratory, clinical, and syndromic data capture the impact of RSV activity, yet did not provide insight into the proposed