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.

table). In accordance with previous studies,[1,3] neutralisation of BA.4/5$_{pp}$ was reduced compared with B.1$_{pp}$ (by between 3·5 times and 11·5 times). Neutralisation of BA.4/5 (R346T, R346S, or R346S) S)$_{pp}$ and BA.4.6$_{pp}$ was even further reduced compared with BA.4/5$_{pp}$ (by around two times), suggesting that mutations (R346T, R346S, or R346S) further extend the already high neutralisation evasion potential of BA.4 and BA.5 sublineages (appendix p 3).

Our data indicate that emerging BA.4 and BA.5 sublineages harbouring S-protein mutations (R346T, R346S, or R346S) have further extended their capacity to evade neutralisation. As a consequence, the availability of therapeutic antibodies for the treatment of individuals infected with such viruses is further reduced, and infections in triple-vaccinated individuals might become increasingly frequent.

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See **Online** for appendix

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Resistance of SARS-CoV-2 omicron subvariant BA.4.6 to antibody neutralisation

SARS-CoV-2, the causative agent of the COVID-19 pandemic, continues to evolve. A subvariant of SARS-CoV-2 omicron (B.1.1.529), known as BA.4.6, emerged in March, 2022, and it appears to be expanding its coverage even in the presence of BA.5, the globally dominant subvariant in recent months (appendix p 2).[1,2] Compared with subvariants BA.4 and BA.5 (hereafter referred to as BA.4/5), BA.4.6 contains two additional mutations, R346T and N658S, in the spike protein (appendix p 2). Three other nascent omicron subvariants with similar spike mutations, BA.4.7 with R346S, BA.5.9 with R346I, and BF.7 with R346T, have also been detected, although at very low frequencies (appendix p 2). The fact that these four new subvariants all have mutations at the R346 residue raises concerns for further antibody evasion, because R346K in a previous subvariant of omicron (BA.1.1) impaired the potency of several therapeutic monoclonal antibodies (mAbs).[3,4]

We aimed to characterise viral receptor affinities and antibody evasion properties of the newly emerging subvariants of BA.4/5. First, we examined whether the transmission advantage of BA.4.6 could be due to a higher affinity for the viral receptor. We measured the affinity of the binding of purified spike trimers of D614G, BA.2, BA.4/5, BA.4.6, BA.4.7, BA.5.9, and BF.7 to dimeric human ACE2 by surface plasmon resonance (appendix p 3). All the spike proteins from BA.4/5 sublineages, and those of BA.4/5 carrying point mutations of R346S and N658S, showed similar binding affinities to ACE2, with dissociation constant values ranging 0·39–0·49 nM. Therefore, the expansion of BA.4.6 cannot be explained by a higher affinity for human ACE2.

Next, to investigate the antibody evasion properties of BA.4.6, BA.4.7, BA.5.9, and BF.7, we assessed the sensitivity of their corresponding pseudoviruses to neutralisation with serum samples from healthy individuals who had received three doses of a COVID-19 mRNA vaccine BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna; ie, who had received booster doses) and patients with either BA.1, BA.2, or BA.4/5 breakthrough infection after vaccination (figure; appendix p 1). The 50% inhibitory dose (ID$_{50}$) titres of the boosted samples against BA.4.6, BA.4.7, BA.5.9, and BF.7 were similar to that against BA.4/5, with no more than

1·5-fold deviation in the geometric mean values (figure). Likewise, the individual mutations R346S and N658S in the background of BA.4/5 had little effect on the neutralisation profiles. A similar trend in serum neutralisation was also observed for BA.1 and BA.4/5 breakthrough samples, but for the BA.2 breakthrough samples, BA.4.6 was slightly (1·3-fold) but significantly (p<0·01) more resistant than BA.4/5; although whether this marginal difference could explain the recent expansion of BA.4.6 worldwide remains unclear. Notably, in BA.4/5 breakthrough cohorts, neutralising titres against new emerging omicron subvariants were higher than those of the serum samples from BA.1 and BA.2 breakthrough cohorts.

To further characterise the antigenic properties of BA.4.6, along with BA.4.7, BA.5.9, and BF.7, we measured the sensitivity of each subvariant pseudovirus to neutralisation by a panel of 23 mAbs that retained potency against earlier omicron subvariants, including some that targeted different epitope clusters (classes 1, 2, 3, and 4) of the receptor-binding domain (RBD)

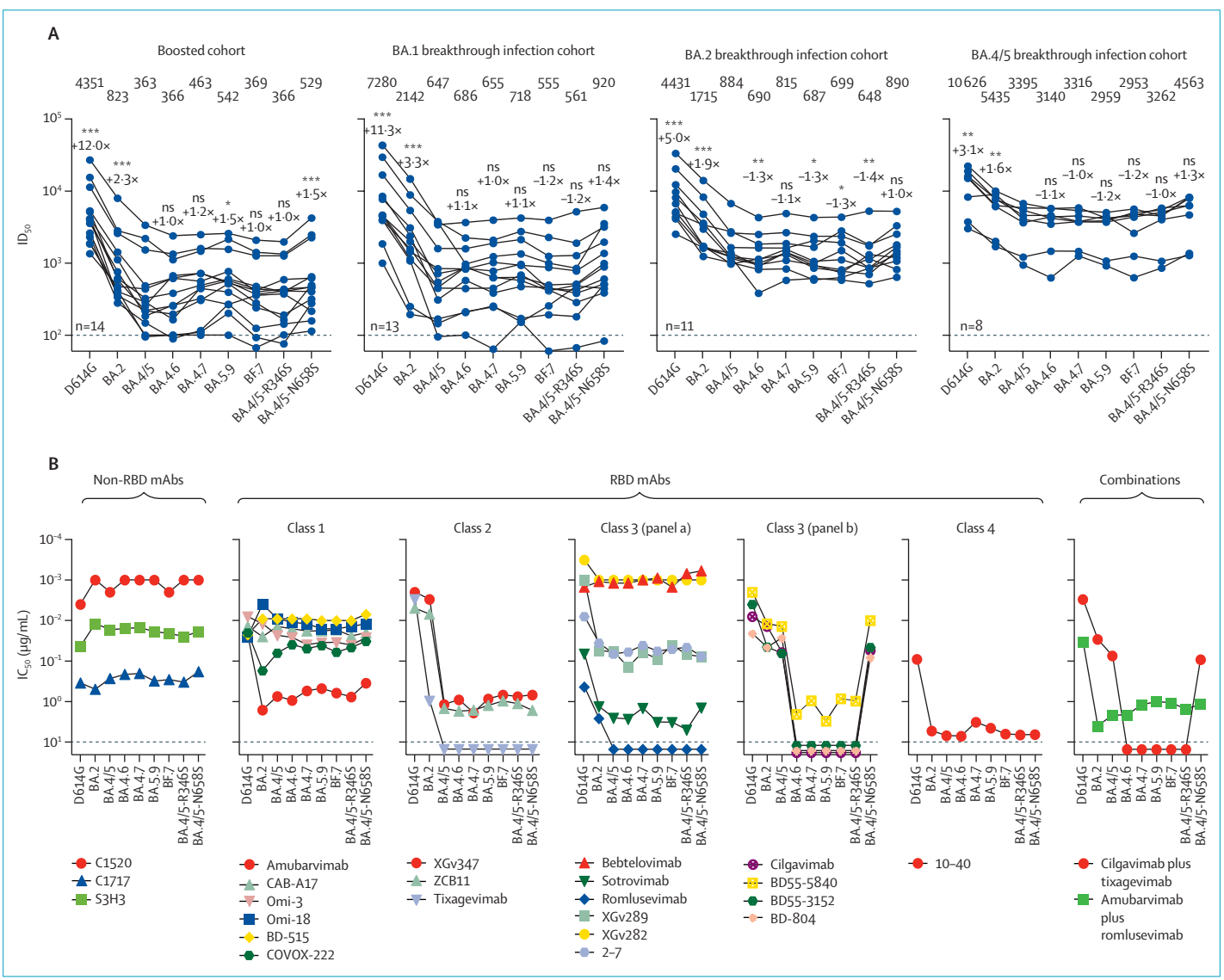
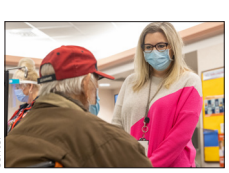


Figure: **Antibody neutralisation profiles of new omicron subvariants**
(A) Neutralisation ID_{50} titres of serum samples from cohorts who were healthy and had received a booster vaccination and who have been vaccinated (some having received a booster) and had BA.1 breakthrough infections, BA.2 breakthrough infections, and BA.4/5 breakthrough infections. Numbers along the top of the graph are the geometric mean ID_{50} values, the values closest to the datapoints are the fold-change in geometric mean ID_{50} from that of BA.4/5, and values on the lower left of each plot indicate the sample size (n). The limit of detection is 100 (dotted line). Comparisons were made against BA.4/5 using the two-tailed Wilcoxon matched-pairs signed-rank tests. (B) Neutralisation by mAbs of pseudotyped D614G, omicron subvariants, and point mutants in the background of BA.4/5. Datapoints above the maximum antibody concentration tested (10 μg/mL, indicated by the dotted line) are arbitrarily plotted to allow for visualisation of each sample. Preclinical mAbs are denoted by their laboratory designations, and clinical mAbs are denoted by their generic names. The combination of cilgavimab and tixagevimab is marketed as Evusheld. IC_{50}=50% inhibitory concentration. ID_{50}=50% inhibitory dose. mAbs=monoclonal antibodies. NS=not significant. RBD=recptor binding domain. *p<0·05. **p<0·01. ***p<0·001.

of the viral spike and others that target non-RBD epitopes (figure; appendix p 4). In general, the neutralisation profiles of BA.4.6, BA.4.7, BA.5.9, and BF.7 did not differ much from that of BA.4/5. The only exceptions were mAbs in RBD class 3 (figure B), which showed substantial reduction in their neutralisation potency against the new subvariants. This loss of neutralising activity was due to mutation R346T, R346S, or R346I, but not due to N658S. Structural analyses revealed that R346T, R346S, or R346I mutations eliminated or weakened hydrogen bonds or salt bridges, or both, between R346 and some RBD class 3 mAbs (appendix p 5), explaining why these mutations led to substantial neutralisation resistance. These findings suggest that BA.4.6, BA.4.7, BA.5.9, and BF.7 probably emerged under the selective pressure of RBD class 3 antibodies in infected individuals.

Importantly, several mAbs in clinical use were also included in the neutralisation assays against the new omicron subvariants (figure; appendix p 6). The combination of cilgavimab and tixagevimab, which had received emergency use authorisation for the prevention of COVID-19,[5] could not neutralise BA.4.6, BA.4.7, BA.5.9, or BF.7, nor the authentic BA.4.6 (appendix p 6). The loss of this antibody combination against BA.4.6 leaves bebtelovimab as the only therapeutic mAb that retained potent activity against all circulating forms of SARS-CoV-2.

As the COVID-19 pandemic and SARS-CoV-2 continue to evolve, our arsenal of authorised monoclonal antibodies might soon be depleted, thereby jeopardising the wellbeing of millions of immunocompromised individuals who cannot robustly respond to COVID-19 vaccines.



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New boosters are here! Who should receive them and when?

The FDA has authorised bivalent booster vaccines containing mRNA for the ancestral SARS-CoV-2 variant as well as B.1.1.529.4 (BA.4) and B.1.1.529.5 (BA.5), the latter being the most prevalent omicron subvariant circulating now.

The US CDC recommends everyone 12 years and older receive these bivalent boosters at least 2 months after their last vaccine dose, regardless of number of previous boosters.

Is this the best strategy based on what we know from boosters with the ancestral spike? The Qatar results demonstrate strong protective effects of a single booster against severe disease with omicron subvariants B.1.1.529.1 (BA.1) and B.1.1.529.2 (BA.2).[1] In a Singapore study, a single booster provided additional protection against severe disease for at least 6 months.[2] A study in Israel of the effectiveness of nirmatrelvir showed that, in an age-stratified immune population during the omicron era, risk of hospitalisation was low in people aged 40–64 years (approximately 15 hospitalisations per 100 000 person-days regardless of nirmatrelvir treatment), although the risk in those aged 65 years or older was significantly lowered by administering nirmatrelvir (58·9 hospitalisations per 100 000 person-days without treatment compared with 14·7 hospitalisations per 100 000 person-days with treatment).[3] Finally, a recent study among 30 million individuals in the UK demonstrates that boosters reduced severe disease after two vaccines doses in the following risk groups: aged 80 years or older, and having five or more comorbidities, being on immunosuppressants, or having chronic kidney disease. This study allows us to understand who will likely need ongoing boosting for COVID-19.[4]

Given all of the data showing strong protection of boosters with the previous mRNA vaccines against severe disease, we believe that upcoming human data will probably show that the bivalent boosters have efficacy similar to or better than the original booster (given the improved antigen match with currently circulating strains). Therefore, we recommend this omicron-specific booster for people 65 years and older, those who are immunocompromised, and those with multiple comorbidities. Because B cells