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Omicron BQ.1 and BQ.1.1 escape neutralisation by omicron subvariant breakthrough infection

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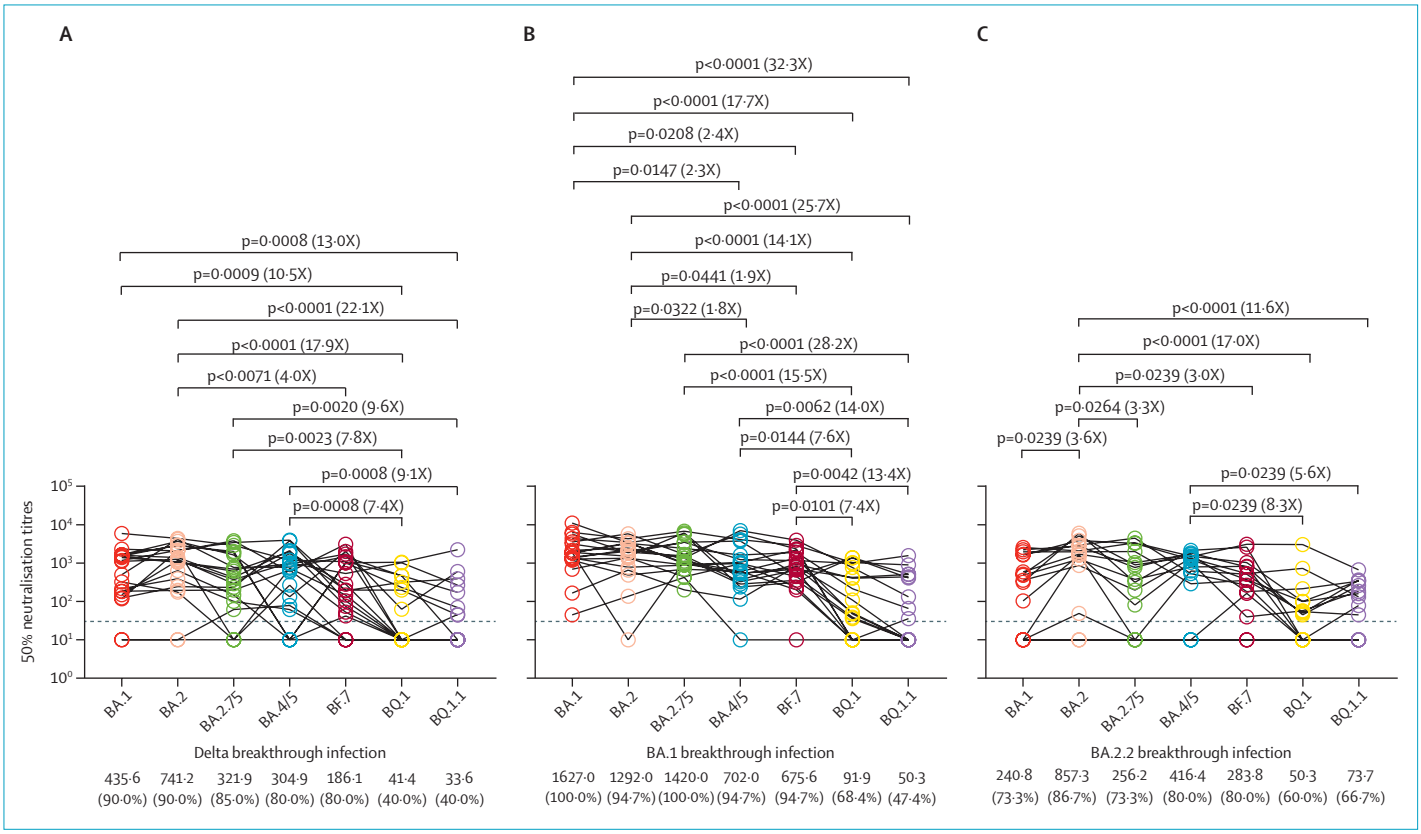
Although the SARS-CoV-2 omicron (BA.1 or B.1.1.529) subvariant BA.5 is dominant worldwide, several new subvariants, including BQ.1, BQ.1.1, BF.7, and BA.4.6, are appearing more frequently in sequenced SARS-CoV-2 infections,[1,2] raising the concern of additional escape neutralisation by antibodies elicited by vaccination or infection. We examined the degree of neutralising antibody escape by omicron subvariants BQ.1, BQ.1.1, BF.7, BA.1, BA.2, BA.2.75, and BA.4 and BA.5 (hereafter referred to as BA.4/5), using 50% neutralisation titres of six serum panels from individuals who had previously had delta BA.1 and BA.2.2 breakthrough infections and more recently had BA.5.1.2, BA.2.76, and BF.7 breakthrough infections (appendix p 2–4, 6).

We first examined the resistance of these omicron subvariants to serum samples from 20 individuals with delta breakthrough infections (appendix p 6). We observed a similar neutralisation activity between BQ.1 and BQ.1.1 but a significantly higher neutralisation resistance compared with BA.1, BA.2, BA.2.75, and BA.4/5; and only 40% of serum samples neutralised BQ.1 and BQ.1.1 (figure A). Specifically, BQ.1 showed a substantially lower neutralisation sensitivity compared with BA.1 (10·5 fold), BA.2 (17·9 fold), BA.2.75 (7·8 fold), and BA.4/5 (7·4 fold); and BQ1.1 showed a lower neutralisation sensitivity compared with BA.1 (13·0 fold), BA.2 (22·1 fold), BA.2.75 (9·6 fold), and BA.4/5 (9·1 fold) (figure A). The serum neutralisation activity was similar against BA.1, BA.2, BA.2.75, BA.4/5, and BF.7, and more than 80% of serum samples neutralised these subvariants (figure A). In addition, BF.7 showed a neutralisation sensitivity 4·0 fold lower than BA.2 (figure A).

Next, we examined the resistance of omicron subvariants to neutralisation by serum samples from individuals



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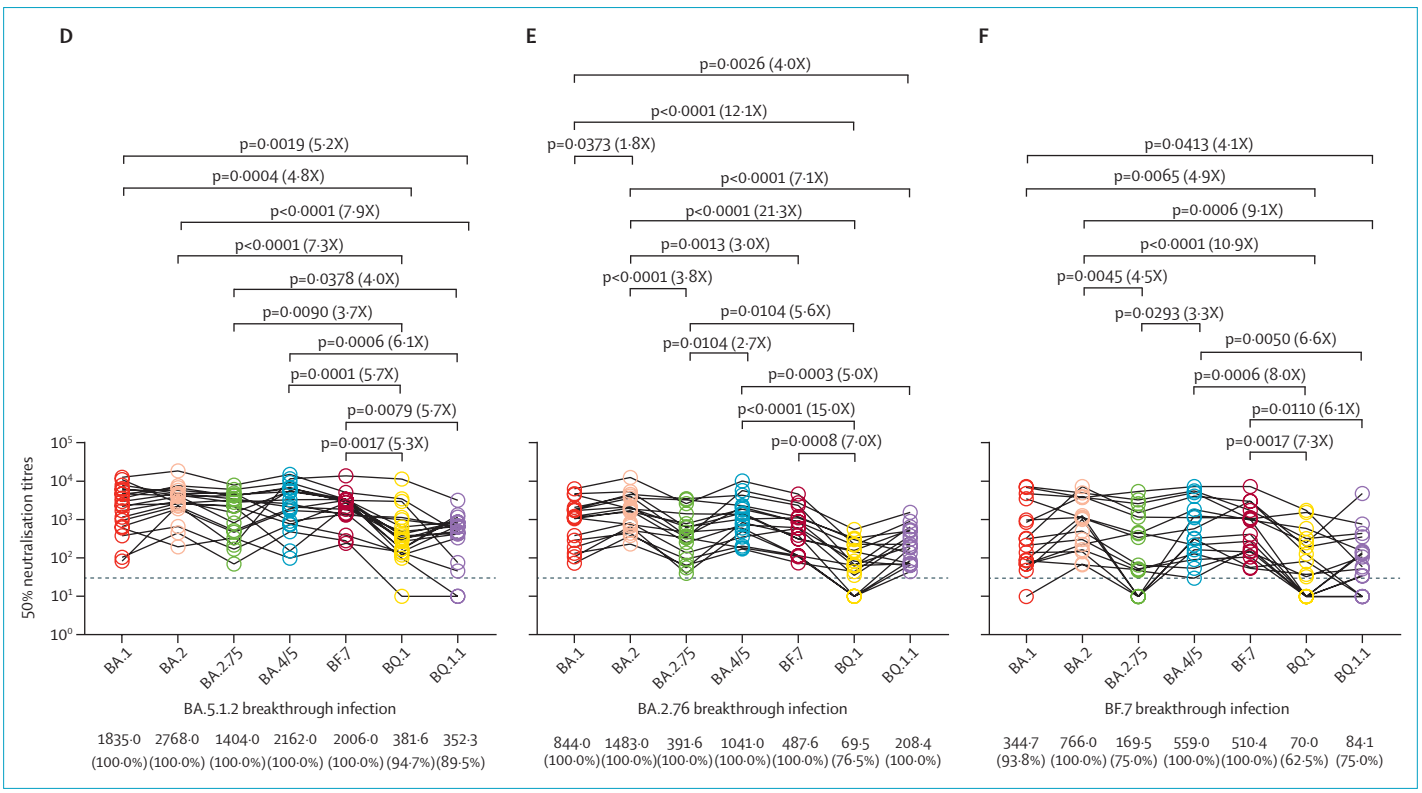

Figure: **Neutralisation of omicron subvariants by serum samples from individuals with delta and omicron subvariant breakthrough infections**
Neutralisation of omicron subvariants, determined by 50% neutralisation titres, by 20 serum samples collected from individuals with delta breakthrough infections (A), 19 serum samples collected from individuals with BA.1 breakthrough infections (B), 15 serum samples collected from individuals with BA.2.2 breakthrough infections (C), 19 serum samples collected from individuals with BA.5.12 breakthrough infections (D), 17 serum samples collected from individuals with BA.2.76 breakthrough infections (E), and 16 serum samples collected from individuals with BF.7 breakthrough infections (F). The horizontal dotted line in all graphs represents a limit of detection of 30, and serum samples with a neutralisation of less than 30 are plotted as 10. The geomatic mean titres and the percentage of individuals with 50% neutralisation titres values above the limit of detection are shown at the bottom of the graph. The fold-change of the geometric mean titre is denoted in brackets. A two-tailed Friedman test with a false discovery rate for multiple comparisons was performed.

with BA.1 (n=19) or BA.2.2 (n=15) breakthrough infections (appendix p 6). We found that BA.1 serum samples more efficiently neutralised BA.2, BA.2.75, BA.4/5, and BF.7 compared with a delta breakthrough infection, and more than 90% of serum samples neutralised these subvariants (figure B). However, neutralisation activity against BQ.1 was substantially decreased compared with BA.1 (17·7 fold), BA.2 (14·1 fold), BA.2.75 (15·5 fold), BA.45 (7·6 fold), and BF.7 (7·4 fold); and was also substantially decreased against BQ.1.1 compared with BA.1 (32·3 fold), BA.2 (25·7 fold), BA.2.75 (28·2 fold), BA.45 (14·0 fold), and BF.7 (13·4 fold; figure B). In addition, neutralisation activity against BA.4/5 was substancially reduced compared with the neutralisation activity against BA.1 (2·3 fold) and BA.2 (1·8 fold); and the neutralisation activity against BF.7 was substantially reduced compared with the neutralisation activity against BA.1 (2·4 fold) and BA.2 (1·9 fold). In contrast, BA.2.2 serum samples less efficiently neutralised BA.1, BA.2.75, BA.4/5, and BF.7, and approximately 80% of all serum samples neutralised these variants. Similarly, BQ.1 and BQ.1.1 were the most resistant subvariants, and only approximately 60% of serum samples were susceptible to them, with a 17-fold reduction in geometric mean titres for BQ.1 and 11·6-fold reduction for BQ.1.1 compared with BA.2 (figure C).

We next examined serum samples from individuals infected with BA.5.1.2 (n=19), BA.2.76 (n=17), or BF.7 (n=16) (appendix p 6). We observed an overall improvement in the neutralising antibody titre, and all serum samples of the three panels neutralised BA.1, BA.2, BA.2.75, BA.4/5, and BF.7, except for serum samples one and four from individuals infected with BF.7, which showed complete loss of neutralising ability against BA.1 and BA.2.75 (figure D–F). Similarly, BQ.1 and BQ.1.1 were significantly resistant to neutralisation, although most serum samples could neutralise these subvariants (figure D–F). We found that the serum samples of a BA.5.1.2 breakthrough infection could not only efficiently neutralise BA.1, BA.2, BA.2.75, and BF.7, but also the majority of these serum samples could neutralise BQ.1 (94·7%) and BQ.1.1 (89·5%), although the neutralisation sensitivity against BQ.1 and BQ.1.1 was significantly lower than other

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tested variants (figure D). Additionally, BA.1, BA.2, BA.4/5, and BF.7 exhibited susceptibility to BA.2.76 breakthrough infection serum samples; however, BA.2.75 showed more resistance than BA.2 and BA.4/5 (figure E). Moreover, BA.2.75 is more resistant to breakthrough BF.7 infection neutralisation than BA.2 and BA.4/5. Further comparisons showed that BA.5.1.2 breakthrough infections induced a broader antibody response against the tested subvariants and induced significantly higher geometric mean titres against BQ.1 and BQ.1.1 compared with delta, BA.1, BA.2.2, BA.2.76, or BF.7 breakthrough infections (figure; appendix p 7).

Omicron subvariants BQ.1 and BQ.1.1 with increased resistance to neutralising antibodies can pose a challenge to immunity induced by vaccination or infection and render therapeutic monoclonal antibodies ineffective.[3-6] Our results suggest that BQ.1 and BQ.1.1 extensively, but incompletely, escape omicron subvariant breakthrough infection neutralisation, including the most recent BA.5.1.2, BA.2.76, and BF.7 infections. However, serum samples of BA.5.1.2 breakthrough infection were effectively neutralised by BQ.1 and BQ.1.1, suggesting that previous BA.5 breakthrough infection might prevent BQ.1 and BQ.1.1, and BQ.1 and BQ.1.1 might not completely replace BA.5.

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Humoral immune evasion of the omicron subvariants BQ.1.1 and XBB

The omicron (B.1.1.529) variant of SARS-CoV-2 evolved into several sublineages, three of which (BA.1, BA.2, and BA.5) became globally dominant. Currently, the prevalence of omicron subvariants BQ.1 (a subvariant of BA.5), its sublineage BQ.1.1, and XBB (a recombinant of two different BA.2 subvariants) is increasing rapidly in the USA, France, Singapore, India, and elsewhere. BQ.1.1 and XBB possess substitutions relative to BA.5 and BA.2, respectively, in the receptor-binding domain of their spike protein (appendix p 4), which is the major target for vaccines and therapeutic monoclonal antibodies (mAbs) for COVID-19. Both variants have the substitution R346T, which confers resistance to certain therapeutic antibodies,[1] raising concerns that mAbs or vaccines might be less effective against BQ.1.1 and XBB than against other omicron strains. We showed that BQ.1.1 and XBB have enhanced immune evasion capabilities compared with earlier omicron variants, including BA.5 and BA.2, by evaluating the efficacy of therapeutic mAbs against BQ.1.1 and XBB.[2] However, the neutralising ability of plasma from convalescent individuals and COVID-19 vaccinees against BQ.1.1 and XBB clinical isolates remained unknown.

Accordingly, we evaluated the neutralising ability of antibodies in plasma from three different groups against BQ.1.1 and XBB clinical isolates: individuals (180–189 days after the third dose; n=20) who received three doses of the monovalent mRNA vaccine BNT162b2 (Pfizer–BioNTech) or mRNA-1273 (Moderna), or both; individuals (33–57 days after the fourth dose; n=20) who received four doses of the monovalent mRNA vaccine BNT162b2 or mRNA-1273, or both; and individuals (29–89 days after the infection; n=10) who received three doses of monovalent BNT162b2 or mRNA-1273 before the BA.2 breakthrough infection. Using a live-virus neutralisation assay, we determined the 50% focus reduction neutralisation titre ($FRNT_{50}$) of the plasma samples against BA.2 (hCoV-19/Japan/UT-NCD1288-2N/2022), BA.5 (hCoV-19/Japan/TY41-702/2022), BQ.1.1 (hCoV-19/Japan/TY41-796/2022), and XBB (hCoV-19/Japan/TY41-795/2022). For plasma from individuals who received a third dose of the mRNA vaccine, 17 (85%) of 20 samples or 18 (90%)