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1 Feikin DR, Higdon MM, Abu-Raddad LJ, et al. Duration of effectiveness of vaccines against SARS-CoV-2 infection and COVID-19 disease: results of a systematic review and meta-regression. *Lancet* 2022; **399:** 924–44.
2 Feikin DR, Abu-Raddad LJ, Andrews N, et al. Assessing vaccine effectiveness against severe COVID-19 disease caused by omicron variant. Report from a meeting of the World Health Organization. *Vaccine* 2022; **40:** 3516–27.

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Omicron subvariants escape antibodies elicited by vaccination and BA.2.2 infection

The BA.1, BA.2, and BA.3 omicron subvariants of SARS-CoV-2 showed similar but substantial resistance to vaccine-induced and infection-induced serum neutralising activity.[1,2] The new BA.2.12.1, BA.2.13, BA.4, and BA.5 omicron subvariants containing Leu452 substitutions show more infectious potential than BA.2.[3] We examined neutralising activity against the BA.1, BA.2, BA.2.11, BA.2.12.1, BA.2.13, BA.4, and BA.5 omicron subvariants in serum from people who received BBIBP-CorV (Sinopharm) primary immunisation, people who received BBIBP-CorV or ZF2001 (Anhui Zhifei Longcom) boosters, and people with omicron breakthrough infections (appendix pp 4, 7).

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25 individuals received two doses of BBIBP-CorV. Using an in-house pseudovirus neutralisation assay we found that two BBIBP-CorV doses induced detectable neutralising antibodies against spike protein mutation D614G in 21 (84%) individuals, but neutralising activity against omicron subvariants (BA.1, BA.2, BA.2.11, BA.2.12.1, BA.2.13, and BA.4/BA.5) was not or only minimally detectable (appendix pp 2–3, 8).

Geometric mean titres (GMTs) of neutralising antibodies against D614G in the 25 individuals who received a BBIBP-CorV booster were 3·1-times higher than in people who received two doses of BBIBP-CorV; the 30 people who received a ZF2001 booster had a 2·9-times higher GMT than individuals who received two doses of BBIBP-CorV (appendix pp 2–3, 8). Neutralising activity against omicron subvariants was observed in 24–48% of people who received a BBIBP-CorV booster and 30–53% of people who received a ZF2001 booster (appendix pp 2–3, 9). Moreover, serum samples with neutralising antibody titres higher than the limit of detection (limit of detection was 30) against the omicron subvariants had lower neutralising activity, with a 4·6–17·1-times lower GMT than the GMT against D614G (appendix pp 2–3). The BA.2.12.1 subvariant showed significantly more resistance than the BA.2 subvariant to a BBIBP-CorV booster (appendix p 9), and the BA.2.11, BA.2.12.1, and BA.2.13 subvariants showed significantly more resistance than the BA.2 subvariant to a ZF2001 booster (appendix p 9). The serum neutralising antibody titres against all tested pseudoviruses did not differ between people who received a BBIBP-CorV booster and those who received a ZF2001 booster (appendix pp 8–9).

18 people had BA.1 breakthrough infection and 15 people had BA.2.2 breakthrough infection (appendix pp 2–3, 7). People with BA.1 breakthrough infection had neutralising titres against omicron subvariants similar to neutralising titres against D614G except for BA.4/BA.5, which had a 2·8-times lower titre compared with D614G-mutated variants (appendix pp 2–3). Antibody titres against omicron subvariants BA.2, BA.2.11, BA.2.12.1, BA.2.13, and BA.4/BA.5 were similar to antibody titres against BA.1 (appendix pp 2–3). Additionally, neutralising antibodies against omicron subvariants above the limit of detection accounted for 88–100% of infections. By contrast, BA.2.2 breakthrough infections had small increases in GMTs against BA.1 compared with BA.1 breakthrough infections (appendix p 10), and neutralising titres against all omicron subvariants, except BA.2, were significantly decreased (3·5–7·4 times) compared with the titres against D614G (appendix pp 2–3). BA.2.2 breakthrough infection resulted in 73–87% of individuals having neutralising antibodies against omicron subvariants higher than the limit of detection (appendix pp 2–3), but neutralising antibody titres against BA.2 were significantly higher than other omicron subvariants (appendix pp 2–3). People with BA.1 breakthrough infections had significantly higher neutralising antibody titres against the BA.1 and BA.2.13 subvariants than people with BA.2.2 breakthrough infections (appendix p 10). Of note, compared with the people with a BA.1 breakthrough infection, people with BA.2.2 breakthrough infections included a substantially higher number of individuals who were triple vaccinated (appendix p 7).

Completion of the primary BBIBP-CorV vaccination schedule induces neutralising antibodies in most individuals against SARS-CoV-2 variants with a D614G mutation, which is consistent with previous studies.[4–6] However, the spike protein mutation enables the escape of omicron subvariants from neutralisation, which can be partly restored by a booster vaccination. Breakthrough omicron infections enhance sera neutralising potential specifically against the omicron subvariants, which is

consistent with two recent studies.[7,8] Together, our results indicate that the new SARS-CoV-2 subvariants (eg, BA.2.12.1 and BA.4 and BA.5) could cause a new wave of infections.

We declare no competing interests. LY, K-LZ, X-LJ, X-JW, and B-DZ contributed equally.

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1 Arora P, Zhang L, Krüger N, et al. SARS-CoV-2 omicron sublineages show comparable cell entry but differential neutralization by therapeutic antibodies. *Cell Host Microbe* 2022; published online May 6. https://doi.org/10.1016/j.chom.2022.04.017.

2 Evans JP, Zeng C, Qu P, et al. Neutralization of SARS-CoV-2 omicron sub-lineages BA.1, BA.1.1, and BA.2. *Cell Host Microbe* 2022; published online April 25. https://doi.org/10.1016/j.chom.2022.04.014.

3 Chen C, Nadeau S, Yared M, et al. CoV-Spectrum: analysis of globally shared SARS-CoV-2 data to identify and characterize new variants. *Bioinformatics* 2021; **38:** 1735–37.

4 Macchia A, Ferrante D, Bouzas MB, et al. Immunogenicity induced by the use of alternative vaccine platforms to deal with vaccine shortages in a low- to middle-income country: results of two randomized clinical trials. *Lancet Reg Health Am* 2022; **9:** 100196.

5 Yu X, Wei D, Xu W, et al. Neutralizing activity of BBIBP-CorV vaccine-elicited sera against beta, delta and other SARS-CoV-2 variants of concern. *Nat Commun* 2022; **13:** 1788.

6 Zhang J, Xing S, Liang D, et al. Differential antibody response to inactivated COVID-19 vaccines in healthy subjects. *Front Cell Infect Microbiol* 2021; **11:** 791660.

7 Khan K, Karim F, Ganga Y, et al. Omicron sub-lineages BA.4/BA.5 escape BA.1 infection elicited neutralizing immunity. *medRxiv* 2022; published online May 1. https://doi.org/10.1101/2022.04.29.22274477.

8 Cao Y, Yisimayi A, Jian F, et al. BA.2.12.1, BA.4 and BA.5 escape antibodies elicited by omicron infection. *bioRxiv* 2022; published online May 2. https://doi.org/10.1101/2022.04.30.489997.

Augmented neutralisation resistance of emerging omicron subvariants BA.2.12.1, BA.4, and BA.5

The SARS-CoV-2 omicron (B.1.1.529) variant is highly resistant against antibody-mediated neutralisation due to many mutations in the spike (S) protein.[1] Several omicron subvariants have been detected, with BA.2.12.1 (first detected in the USA) and BA.4 and BA.5 (first detected in South Africa) currently outcompeting the previously circulating BA.1 and BA.2 subvariants in several countries. The S proteins of BA.4 and BA.5, which are identical on the protein level, and BA.2.12.1 harbour unique mutations (appendix pp 1–2), but it is largely unknown whether they differ from BA.1 and BA.2 regarding neutralisation sensitivity.

We analysed neutralisation of BA.2.12.1 and BA.4/BA.5 by monoclonal antibodies and antibodies induced on vaccination or infection, making use of S-protein-bearing reporter viruses, which represent an adequate surrogate model.[2] As a reference, we used particles bearing the S proteins of either B.1 (circulating during the early phase of the pandemic), BA.1, or BA.2. We identified that all omicron subvariants robustly evaded neutralisation by six of ten antibodies, although subvariant-specific differences were noted (appendix pp 1–2). Sotrovimab, which was reported to effectively neutralise BA.1,[1,3] showed markedly reduced neutralisation of BA.2, BA.2.12.1, and BA.4/BA.5 in comparison to neutralisation of BA.1 (appendix pp 1–2). Conversely, cilgavimab showed substantial activity against all omicron subvariants except BA.1. These results are in line with those of Cao and colleagues,[4] whereas Yamasoba and colleagues[5] reported a significant reduction of BA.4/BA.5 neutralisation by cilgavimab in comparison with neutralisation of BA.1. S2H97 showed similar efficacy against all subvariants but required high concentrations for efficient neutralisation. Finally, bebtelovimab (LY-CoV1404) neutralised all subvariants tested with similarly high efficacy (appendix pp 1–2), in agreement with findings reported for BA.1 and BA.2.[6]

We next analysed neutralisation of BA.2.12.1 and BA.4/BA.5 by plasma from ten unvaccinated people in Germany (aged 20–71 years; five male and five female) who had mild infections in March–May, 2022, when BA.1 and, subsequently, BA.2 were circulating in Germany (appendix pp 3–4). BA.1 was neutralised with 2·9-times higher efficiency (measured by the fold difference in 50% neutralisation titre values between plasma pairs) than was B.1, whereas neutralisation of BA.2 was 27·2-times more efficient than of B.1 (appendix pp 1–2), suggesting that most donors were infected with BA.2. Notably, neutralisation of BA.2.12.1 was similar to that of BA.2, whereas BA.4/BA.5 neutralisation was markedly reduced compared with BA.2 and BA.2.12.1 (ie, only 1·6-times higher than B.1; appendix pp 1–2).

We further analysed neutralisation by antibodies induced by vaccination (appendix pp 3–4). We identified that BA.1 and BA.2 evaded neutralisation by antibodies that were induced on triple BNT162b2 (Pfizer-BioNTech) vaccination with similar efficiency (ie, 4·3-times reduced neutralisation for BA.1 and 4·2-times reduced neutralisation for BA.2 compared with B.1), as expected,[7] whereas evasion by BA.2.12.1 (ie, 6·1-times reduced neutralisation compared with B.1) and particularly BA.4/BA.5 (ie, 8·1-times reduced neutralisation compared with B.1) was more efficient (appendix pp 1–2). A similar tendency was also observed for samples taken from individuals who had been triple vaccinated with BNT162b2 with subsequent BA.1 or BA.2

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