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.

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.

*Lin Yao, Ka-Li Zhu, Xiao-Lin Jiang, Xue-Jun Wang, Bing-Dong Zhan, Hui-Xia Gao, Xing-Yi Geng, Li-Jun Duan, Er-Hei Dai, *Mai-Juan Ma*
mjma@163.com

State Key Laboratory of Pathogen and Biosecurity, Beijing Institute of Microbiology and Epidemiology, Beijing, China (LY, K-LZ, X-JW, L-JD, M-JM); Department of Epidemiology and Biostatistics, School of Public Health, Anhui Medical University, Hefei, China (LY, K-LZ, M-JM); Shandong Provincial Key Laboratory of Infectious Disease Control and Prevention, Shandong Provincial Center for Disease Control and Prevention, Jinan, China (X-LJ); Department of Laboratory Medicine, Quzhou Center for Disease Control and Prevention, Quzhou, China (B-DZ); Department of Laboratory Medicine, The Fifth Hospital of Shijiazhuang, Hebei Medical University, Shijiazhuang, China (H-XG, E-HD); Department of Infectious Disease Control and Prevention, Jinan Center for Disease Control and Prevention, Jinan, China (X-YG)

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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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breakthrough infection (appendix pp 1–4).

Here, we show that bebtelovimab should represent an effective treatment for patients with COVID-19, irrespective of the infecting omicron subvariant, in keeping with bebtelovimab recognising a highly conserved epitope.[8] Further, our findings indicate that immune evasion of BA.2.12.1 is only moderately increased relative to BA.2, suggesting that increased human-to-human transmissibility (eg, due to increased replication in the upper respiratory tract or augmented infection of cells) might contribute to the expansion of BA.2.12.1. Finally, the robust neutralisation evasion by BA.4 and BA.5 indicates that these are immune-evasion variants, which are more adept than BA.1 or BA.2 to spread in populations that are vaccinated or recovering from omicron, or both.

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

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

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See **Online** for appendix

Heterologous booster response after inactivated virus BBIBP-CorV vaccination in older people

Whole-virion inactivated SARS-CoV-2 vaccines are one of the most widely used vaccines worldwide. However, compared with the mRNA-based and adenovirus-based platforms,[1] little information is available about the immune response that is induced by inactivated virus vaccines[2] and the convenience of applying heterologous boosters to reach an improved response against variants of concern, including omicron (B.1.1.529). Particularly scarce are data for older people (ie, age >60 years).

In this study, we performed a longitudinal analysis of serum samples from an older population of volunteers (n=26 for prime vaccination and n=98 for booster vaccination; mean age 79 years [SD 11·8]), obtained 21 days, 100 days, 160 days, and 220 days after the second dose of a two-dose primary immunisation schedule with the inactivated virus BBIBP-CorV (Sinopharm) vaccine, and 21 days and 90 days after application of a booster with ChAdOx1 nCoV-19 (Oxford-AstraZeneca), Sputnik V (Gamaleya Research Institute of Epidemiology and Microbiology), or BNT162b2 (Pfizer-BioNTech). Because of the low seroconversion rates observed after BBIBP-CorV primary vaccination, a homologous booster dose was not included in this study. We evaluated serum concentrations of IgG anti-spike antibodies[3] and neutralising capacity against the original B.1 lineage and the omicron variant of concern.[4]

Both the concentration of IgG anti-spike antibodies and the seropositivity rate greatly declined over time after vaccination with two doses of BBIBP-CorV (figure). After 220 days, the seropositivity rate was reduced from 81% to 54%. Application of a booster dose of ChAdOx1 nCoV-19, Sputnik V, or BNT162b2 raised the concentrations of IgG anti-spike antibodies on day 21 more than 350-fold (from 11·8 binding antibody units [BAU]/mL to 4397 BAU/mL for ChAdOx1 nCoV-19, 4285 BAU/mL for Sputnik V, and 9391 BAU/mL for BNT162b2) and seropositivity was detected in 98 (100%) participants (figure). This response was sustained at 90 days after the booster dose (figure).

Neutralising antibodies against B.1 and omicron also decreased over time since primary immunisation (appendix p 1). Neutralising activity against the B.1 virus was detected in six (23%) of 26 participants at 220 days after vaccination with two doses of BBIBP-CorV (appendix