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.

See Online for appendix

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.

Published Online December 7, 2022 https://doi.org/10.1016/S1473-3099(22)00816-7

X-LJ, K-LZ, and X-JW contributed equally as joint first authors. E-HD and M-JM contributed equally as joint last authors. We declare no competing interests. We thank all study subjects for their participation in our study. This work was supported by grants from the National Natural Science Foundation of China (82273692, 92169207, 81621005, and 81830101), the Beijing Natural Science Foundation (L202038), and the Key Research and Development Plan of Shandong Province (2021RZA01021).

*Xiao-Lin Jiang, Ka-Li Zhu, Xue-Jun Wang, Guo-Lin Wang, Yi-Ke Li, Xue-Juan He, Wen-Kui Sun, Peng-Xiang Huang, Jin-Zhong Zhang, Hui-Xia Gao, Er-Hei Dai, *Mai-Juan Ma*
mjma@163.com

Shandong Provincial Key Laboratory of Infectious Disease Control and Prevention, Shandong Provincial Center for Disease Control and Prevention, Jinan, China (X-LJ, W-KS, P-XH); State Key Laboratory of Pathogen and Biosecurity, Beijing Institute of Microbiology and Epidemiology, Beijing 100071, China (K-LZ, G-LW, Y-KL, X-JH, M-JM); Department of Epidemiology and Biostatistics, School of Public Health, Anhui Medical University, Hefei, China (K-LZ, M-JM); Department of Epidemiology, School of Public Health, Zhengzhou University, Zhengzhou, China (Y-KL, X-JH, M-JM); Department of Infectious Disease Control and Prevention, Liaocheng Center for Disease Control and Prevention, Liaocheng, China (J-ZZ); Department of Laboratory Medicine, The Fifth Hospital of Shijiazhuang, Hebei Medical University, Shijiazhuang, China (H-XG, E-HD)

1 US Department of Health and Human Services, CDC. Prevention CfDCa. COVID data tracker. 2022. https://covid.cdc.gov/covid-data-tracker/#datatracker-home (accessed Nov 7, 2022).
2 GISAID. Genomic epidemiology of SARS-CoV-2 with subsampling focused globally over the past 6 months. 2022. https://gisaid.org/phylodynamics/global/nextstrain/ (accessed Nov 7, 2022).
3 Qu P, Evans JP, Faraone J, et al. Distinct neutralizing antibody escape of SARS-CoV-2 omicron subvariants BQ.1, BQ.1.1, BA.4.6, BF.7 and BA.2.75.2. *bioRxiv* 2022; published online Oct 20. https://doi.org/10.1101/2022.10.19.512891 (preprint).
4 Cao Y, Jian F, Wang J, et al. Imprinted SARS-CoV-2 humoral immunity induces convergent omicron RBD evolution. *bioRxiv* 2022; published online Oct 4. https://doi.org/10.1101/2022.09.15.507787 (preprint).
5 Kurhade C, Zou J, Xia H, et al. Low neutralization of SARS-CoV-2 omicron BA.2.75.2, BQ.1.1, and XBB.1 by 4 doses of parental mRNA vaccine or a BA.5-bivalent booster. *bioRxiv* 2022; published online Nov 2. https://doi.org/10.1101/2022.10.31.514580 (preprint).
6 Miller J, Hachmann NP, Collier A-rY, et al. Substantial neutralization escape by the SARS-CoV-2 omicron variant BQ.1.1. *bioRxiv* 2022; published online Nov 2. https://doi.org/10.1101/2022.11.01.514722 (preprint).

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%)

of 20 samples had $FRNT_{50}$ values that were below the limit of detection (<10-fold dilution) against BQ.1.1 or XBB, respectively. To calculate the geometric mean titre of each group, we assigned samples that were under the limit of detection of an $FRNT_{50}$ value of ten. The $FRNT_{50}$ geometric mean titres against BQ.1.1 and XBB were 21·1-fold and 21·6-fold lower, respectively, than those against the ancestral strain (SARS-CoV-2/UT-NC002-1T/Human/2020/Tokyo) (figure A, appendix p 5). In addition, the geometric mean titres against BQ.1.1 and XBB were 1·7-fold and 2·6-fold lower, respectively, than those against BA.5 and BA.2. Similar results were obtained with samples from individuals who received four doses of mRNA vaccine (figure B); the $FRNT_{50}$ geometric mean titres against BQ.1.1 and XBB were 43·3-fold and 51·6-fold lower, respectively, than those against the ancestral strain, and were 3·7-fold and 6·2-fold lower than those against BA.5 and BA.2, respectively (figure B, appendix p 6). In contrast, most of the samples from vaccinees with BA.2 breakthrough infection neutralised BQ.1.1 and XBB; however, the $FRNT_{50}$ geometric mean titres against BQ.1.1 and XBB were 35·2-fold and 61·7-fold lower, respectively, than those against the ancestral strain, and were 4·9-fold and 15·1-fold lower than those against BA.5 and BA.2, respectively (figure C, appendix p 7).

Our data suggest that the omicron sublineages BQ.1.1 and XBB effectively evade current humoral immunity induced by mRNA vaccines or natural infection. A previous study using pseudotyped viruses reported that BQ.1.1 and XBB were less well recognised than BA.2 and BA.4/5 by plasma from convalescent individuals and mRNA vaccinees.[3] These findings show that BQ.1.1 and XBB clinical isolates have higher immune evasion abilities than earlier omicron variants, including BA.5 and BA.2.

YK is supported by grants from the Center for Research on Influenza Pathogenesis

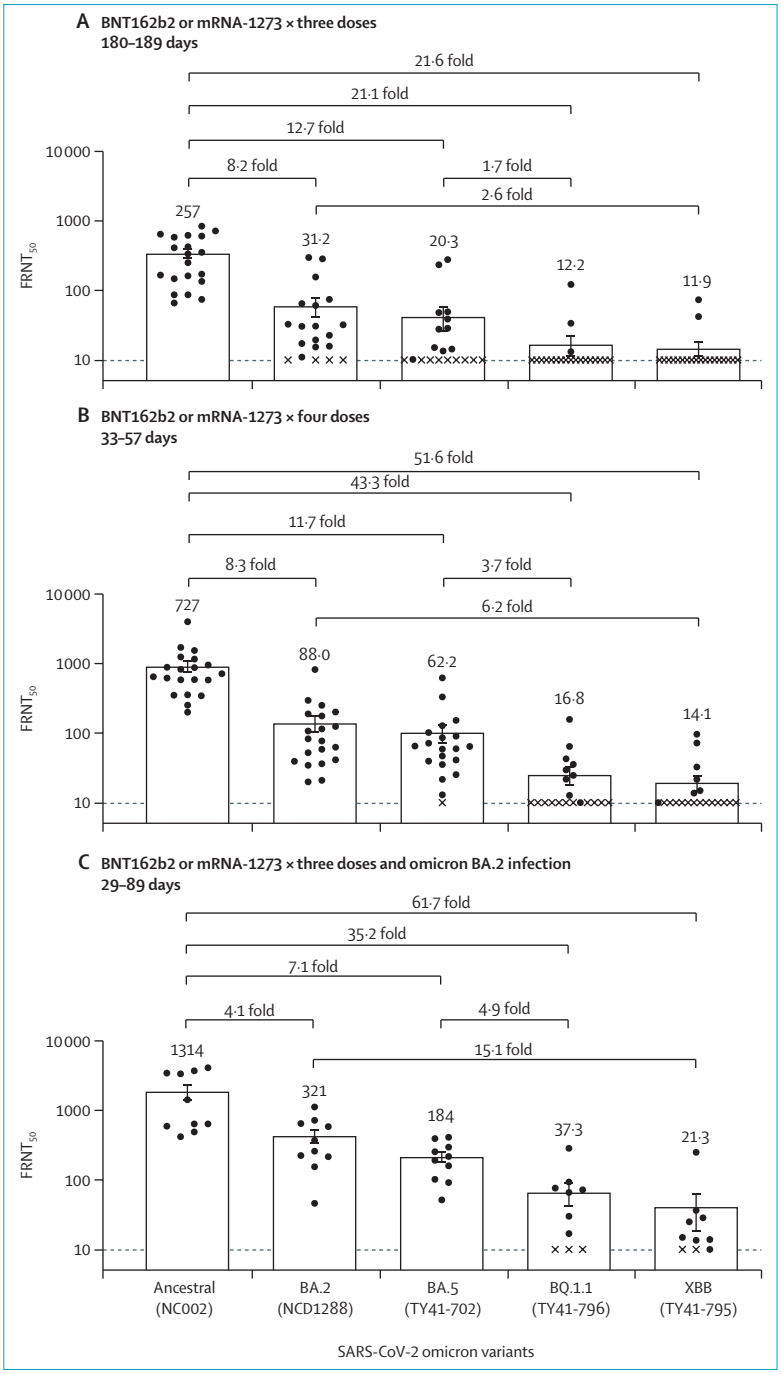

Figure: **Antibody responses to SARS-CoV-2 omicron variants**
(A) Neutralising antibody titres of human plasma obtained from individuals immunised with a third dose of BNT162b2 or mRNA-1273 vaccine. Samples were collected 180–189 days after the third immunisation (n=20). (B) Neutralising antibody titres of human plasma obtained from individuals immunised with four doses of BNT162b2 or mRNA-1273 vaccine. Samples were collected 33–57 days after the fourth immunisation (n=20). (C) Neutralising antibody titres of human plasma obtained from individuals who were infected with omicron BA.2 after three doses of BNT162b2 or mRNA-1273 vaccine. Samples were collected 29–89 days after symptom onset (n=10). Each dot represents data from one individual. The lower limit of detection (value=10) is indicated by the horizontal dashed line. Samples under the detection limit (<10-fold dilution) were assigned an $FRNT_{50}$ value of 10 and are represented by X. Geometric mean titres are shown. $FRNT_{50}$=50% focus reduction neutralisation titre.

(HHSN272201400008C) and from the Center for Research on Influenza Pathogenesis and Transmission (75N93021C00014), funded by the National Institute of Allergy and Infectious Disease; and by a Research Program on Emerging and Reemerging Infectious Diseases (JP21fk0108552 and JP21fk0108615), a Project Promoting Support for Drug Discovery (JP21nf0101632), the Japan Program for Infectious Diseases Research and Infrastructure (JP22wm0125002), and a grant (JP223fa627001) from the Japan Agency for Medical Research and Development. All other authors declare no competing interests. RU, MI, and YF contributed equally.

*Ryuta Uraki, Mutsumi Ito, Yuri Furusawa, Seiya Yamayoshi, Kiyoko Iwatsuki-Horimoto, Eisuke Adachi, Makoto Saito, Michiko Koga, Takeya Tsutsumi, Shinya Yamamoto, Amato Otani, Maki Kiso, Yuko Sakai-Tagawa, Hiroshi Ueki, Hiroshi Yotsuyanagi, Masaki Imai, *Yoshihiro Kawaoka*
yoshihiro.kawaoka@wisc.edu

Division of Virology, Institute of Medical Science (RU, MIt, YF, SeY, KI-H, ShY, MKi, YS-T, HU, MIm, YK), Department of Infectious Diseases and Applied Immunology, IMSUT Hospital of The Institute of Medical Science (EA, MS, MKo, TT, AO, HY), and Division of Infectious Diseases, Advanced Clinical Research Center, Institute of Medical Science (MS, MKo, TT, ShY, HY), University of Tokyo, Tokyo 108-8639, Japan; The Research Center for Global Viral Diseases, National Center for Global Health and Medicine Research Institute, Tokyo, Japan (RU, YF, SeY, HU, MIm, YK); Influenza Research Institute, Department of Pathobiological Sciences, School of Veterinary Medicine, University of Wisconsin–Madison, Madison, WI, USA (YK)

1 Miller NL, Clark T, Raman R, Sasisekharan R. Insights on the mutational landscape of the SARS-CoV-2 omicron variant receptor-binding domain. *Cell Rep Med* 2022; **3:** 100527.
2 Imai M, Ito M, Kiso M, et al. Efficacy of antiviral agents against omicron BQ.1.1 and XBB subvariants. *N Engl J Med* (in press).
3 Cao Y, Jian F, Wang J, et al. Imprinted SARS-CoV-2 humoral immunity induces convergent omicron RBD evolution. *bioRxiv* 2022; published online Sept 16. https://doi.org/10.1101/2022.09.15.507787 (preprint).

For more on **OpenPrescribing** see https://openprescribing.net

See **Online** for appendix

Published **Online** December 7, 2022 https://doi.org/10.1016/S1473-3099(22)00814-3

Antibiotic prescribing in general practice during COVID-19 and beyond

Richard Armitage and Laura B Nellums[1] reported that when accounting for changes in appointment numbers, the total number of antibiotics prescribed between April 1, and Aug 31, 2020, was 6·71% higher than expected—a statistically significant increase.

By use of updated data, we were able to assess whether the increase was sustained throughout the pandemic and beyond. OpenPrescribing publishes monthly data for the number of items prescribed in general practice in England, UK. National Health Service (NHS) England provides monthly data for appointment activity in general practice.[2]

We conducted an interrupted time-series analysis using the negative binomial model and data from Jan 1, 2018, to July 31, 2022. Interruptions were set at the months of March, 2020, the start of the pandemic, and July, 2021, when restrictions were lifted in England, UK. All data and analysis code are available online.[3]

In accordance with Armitage and Nellums,[1] we identified that there was an immediate increase in the mean number of items prescribed per 100 appointments at the start of the COVID-19 pandemic (incidence rate ratio [IRR] 1·14, 95% CI 1·07–1·23). However, the prescribing rate gradually declined from May, 2020, onwards (IRR 0·98, 95% CI 0·97–0·98) and was lower than the expected trend from December, 2020, to July, 2021, coinciding with the third national lockdown, from Jan 5, 2021, to July 19, 2021 (appendix p 1). The lifting of lockdown restrictions in July, 2021, saw an immediate increase in the prescribing rate (IRR 1·21, 95% CI 1·11–1·33), which continued to gradually increase (1·03, 1·02–1·04) until it was in line with the expected trend.

Conversely, the start of the pandemic saw an immediate decrease in the absolute number of antibiotics prescribed (IRR 0·85, 95% CI 0·80–0·91), and the absolute number of antibiotics prescribed remained below the expected trend throughout the period of COVID-19 restrictions, from March, 2020, to July, 2021 (appendix p 1). The lifting of lockdown restrictions in July, 2021, saw an immediate increase in the number of items prescribed (IRR 1·18, 95% CI 1·09–1·29]).

Armitage and Nellums suggested that the increase in antibiotic prescribing was driven by the sharp increase in telephone appointments during the COVID-19 pandemic.[1] The proportion of general practice appointments conducted via telephone, although decreasing, remains high at 31·6% in July, 2022, compared with 14·2% in July, 2019 (appendix p 1). Nevertheless, antibiotic prescribing rates have returned to the expected trend of falling antibiotic consumption in general practice. Our data provide little population-level evidence of an association between telephone appointments and inappropriate antibiotic stewardship, because prescribing rates have continued to decrease despite a high proportion of general practice appointments being conducted via telephone.

Clinicians should still be supported to use antibiotics appropriately. However, when considering the impact of the total pandemic restrictions in England, UK, there is little evidence that COVID-19 has hindered attempts by the NHS to reduce antibiotic prescribing on the whole.[4]

KKCM reports grants from the CW Maplethorpe Fellowship, the UK National Institute for Health Research, the European Commission, AIR@InnoHK administered by Hong Kong Innovation and Technology Commission, and the Research Grant Council, Hong Kong; and reports personal fees from IQVIA, unrelated to this Correspondence. ICKW reports research funding outside the submitted work from Amgen, Bristol Myers Squibb, Pfizer, Janssen, Bayer, GSK, Novartis, the Hong Kong Research Grants Council, the Hong Kong Health and Medical Research Fund, the Hong Kong Innovation and Technology Commission, the UK National Institute for Health Research, the European Commission, and the National Health and Medical Research Council in Australia and received expert testimony payment from the Hong Kong Court of Final Appeal, consultation fees from IQVIA, and speaker fees from Janssen and Medice in the previous 3 years. ICKW is the principal investigator and KKCM is the co-investigator of the project for A Multinational Big Data COVID-19 Epidemiological Study on Post-infection Outcomes (ACESO), funded by the Hong Kong Research Grant Council